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Diels-Alder Reaction of 2-Carbomethoxy-2-cyclohexen-1-one and Its Application to the Synthesis of Petasitolone and Steroidal Compounds

by

Teng Ko Ngooi

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SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled, Diels-Alder Reaction of 2-Carbomethoxy-2-cyclohexen-1-one and Its Application to the Synthesis of Petasitolone and Steroidal Compounds, submitted by Teng Ko Ngooi in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

FOR MY PARENTS

AND

MY SISTERS

Abstract

Under stannic chloride catalysis, 2-carbomethoxy-2-cyclohexen-1-one (I) was found to undergo Diels-Alder reaction with a variety of dienes to give directly the *cis*-1-octalone system possessing a functionalized substituent at the angular position. With unsymmetrically substituted dienes, the resulting angularly substituted adducts were found to be those predicted on the basis of the normal rules (*ortho* and *para*) governing the orientation of Diels-Alder addition. In cases where differing secondary orbital overlap would affect the stereochemistry of the adducts, the major isomer in each case was found to be that produced with secondary overlap of the diene with the ester carbonyl rather than the ketone carbonyl presumably due in part to steric effect. The degree of stereoselectivity was further shown to be dependent upon both the reaction temperature and the diene used and was generally enhanced when the reaction was carried out at lower temperatures and when a bulkier diene was involved.

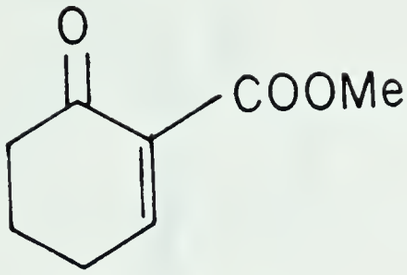
The observations that were made in the study of the Diels-Alder additions of enone-ester **I**, have led to a successful synthesis of petasitolone (**II**), an eremophilane sesquiterpene. The Diels-Alder adduct **III** which was obtained in excellent stereoselectivity in good yield was

converted to the keto-ester **IV** by reduction of its enol-phosphate moiety. Hydride reduction of **IV** furnished diol **V** which was converted to keto-mesylate **VI** by selective mesylation and oxidation. Treatment of **VI** with a mixture of zinc dust and sodium iodide gave the ketone **VII.** Carbomethoxylation of the latter compound gave the keto-ester **VIII** which were reduced with sodium borohydride. A dehydration of the resulting β-hydroxyesters **IX** with dicyclohexylcarbodiimide and a catalytic amount of cuprous chloride led to the unsaturated ester **X.** Allylic oxidation furnished the acetate **XI** which upon treatment with excess methyllithium, followed by oxidation gave petasitolone (**II**).

The final chapter of the thesis describes a rapid preparation of the dienes **XII** and **XIII.** Photocycloaddition of 3-methyl-2-cyclohexen-1-one with excess vinyl acetate gave the chromatographically separable ketones **XIV** and **XV.** Each of these ketones was subjected to vinylmagnesium bromide (or vinyllithium) addition, followed by a dehydration of the resulting alcohols **XVI** and **XVII** _via_ the carbamate derivatives to give the dienes **XII** and **XIII** in 65% and 58% overall yield, respectively. Their Diels-Alder additions to _p_-benzoquinone were examined. The additions proceeded smoothly at -33°C and under stannic chloride catalysis to give the Diels-Alder adducts **XVIII** and **XIX** which were isolated as their triacetate derivatives **XX** and **XXI**, respectively.

In this way, a rapid process for the preparations of some D-nor-steroids was developed. The biological activities of compound **XX** are under current examination.

The Diels-Alder additions of the dienes **XII** and **XIII** to enone-ester **I** were examined with the objective of an efficient generation of adducts **XXII** which could be used for the synthesis of the cardenolide, strophanthidin (**XXIII**). The additions were found to proceed in good yield. However a number of adducts were obtained. One of the major adducts which was believed to have the required stereochemistry for strophanthidin (**XXIII**) synthesis has been subjected to an X-ray analysis so as to provide a definitive structural assignment to this compound.



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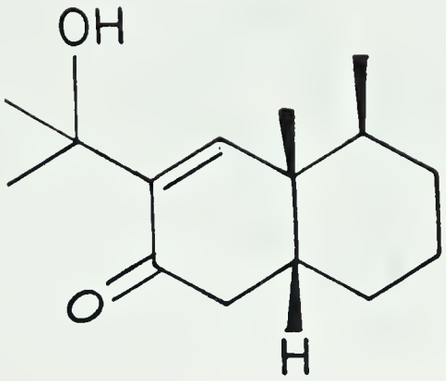

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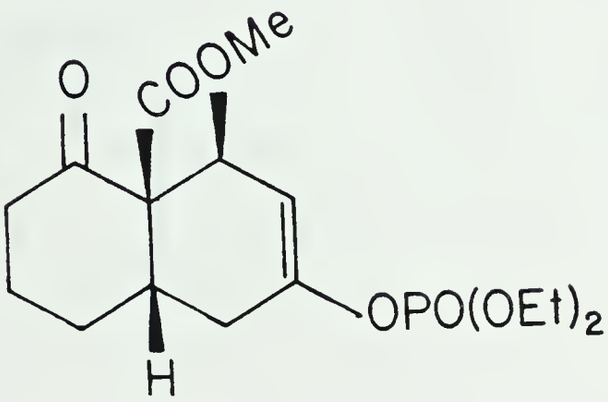

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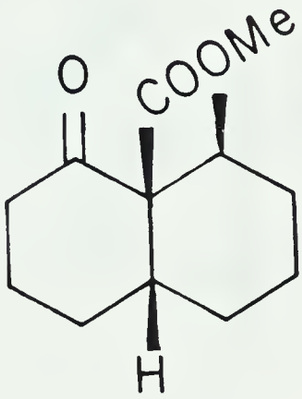

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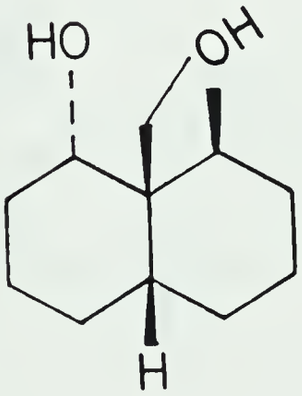

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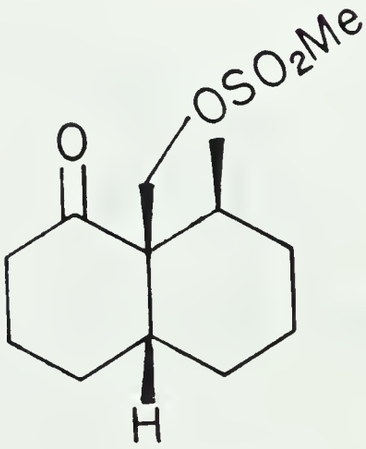

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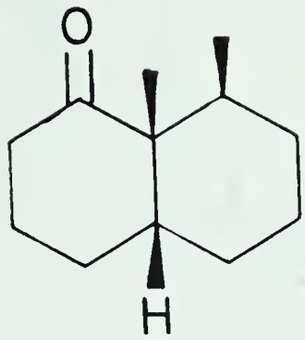

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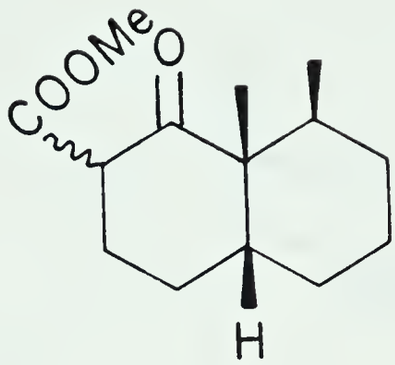

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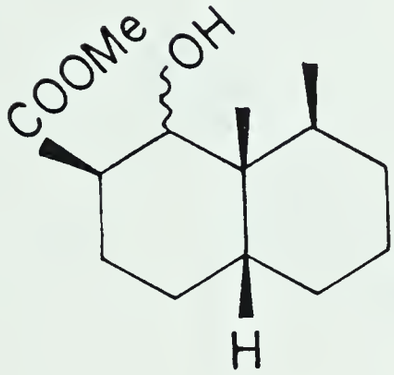

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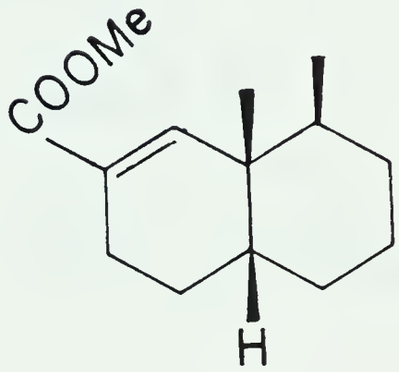

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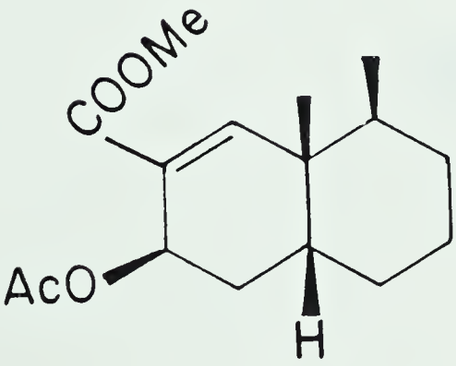

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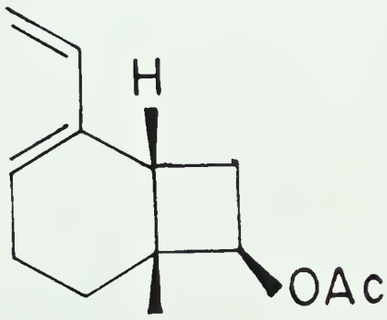

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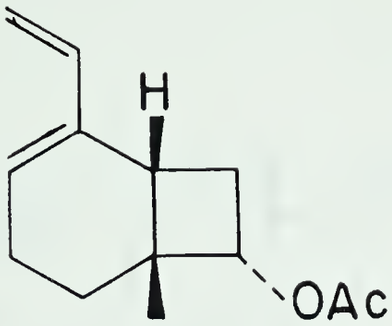

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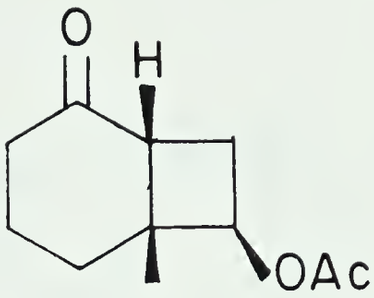

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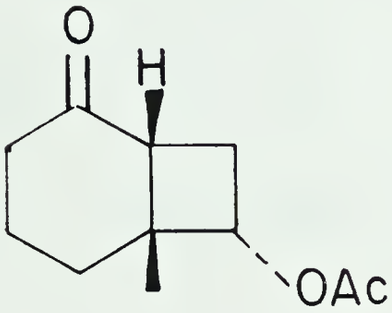

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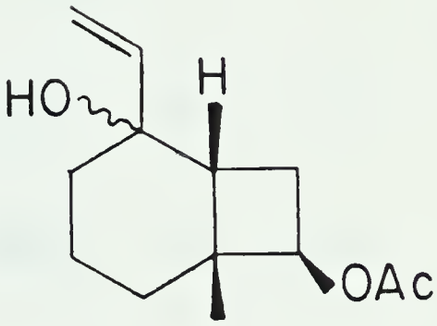

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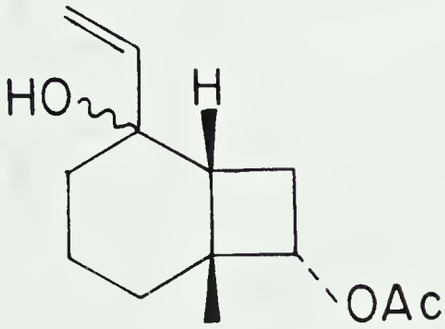

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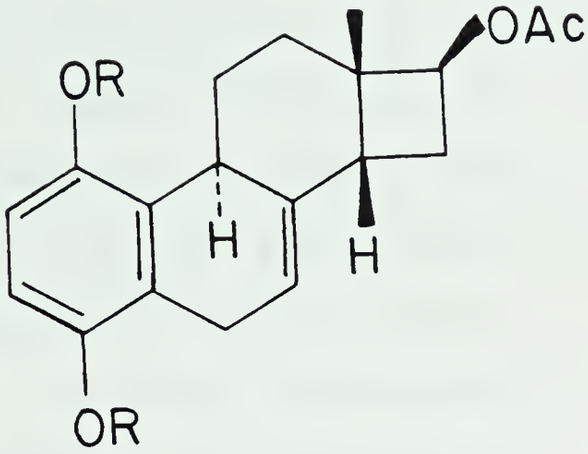
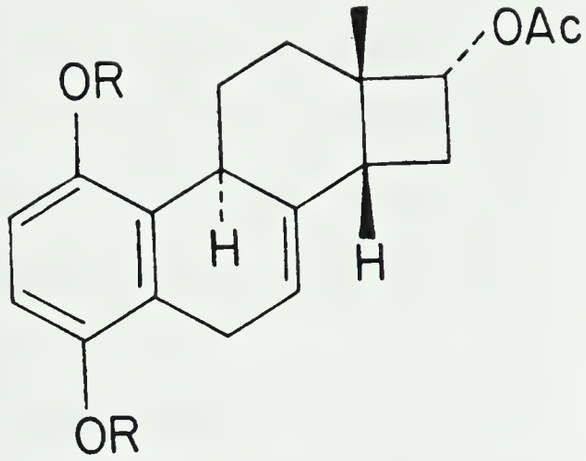


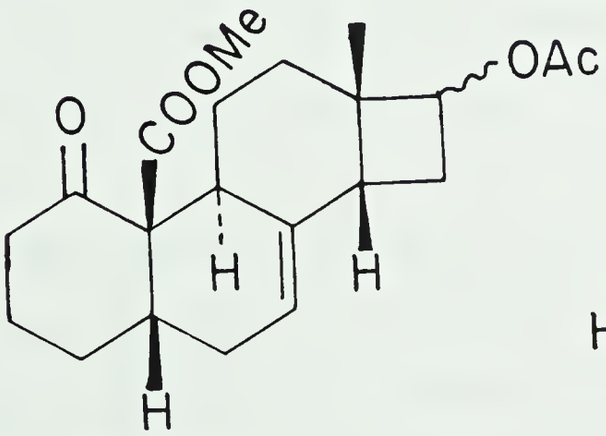


XVIII R = H

XX R = Ac

XIX R = H

XXI R = Ac



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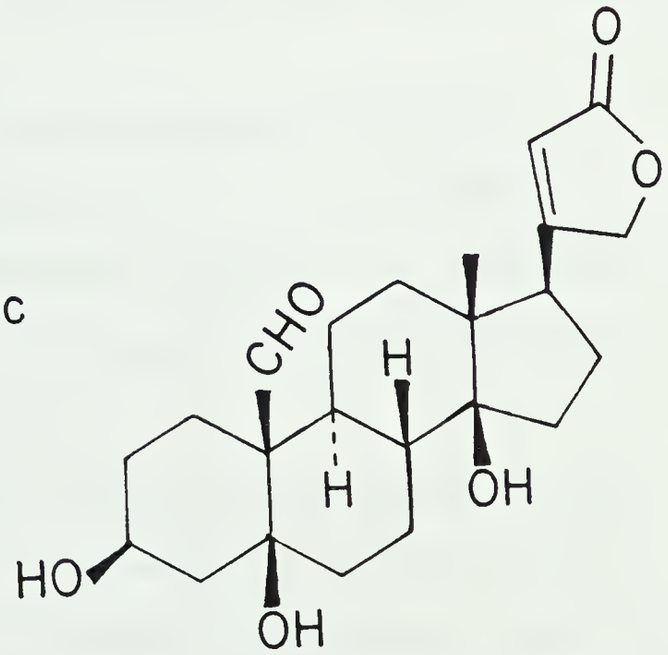

XXIII

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CHAPTER 1.

Diels-Alder Reaction of 2-Carbomethoxy-2-Cyclohexene-1-one

Introduction*

The cycloaddition of dienes with olefins (dienophiles) to give cyclohexenes was first observed by Diels and Alder[13] in 1928 to be a general process. Since that time, the Diels-Alder reaction has gained prominence as a useful methodology for the total synthesis of natural products. For example, the reaction has been used in classical syntheses of cantharidin,[14] cholesterol,[15] cortisone,[16] estrone[17] and reserpine.[18] Although its potential in organic synthesis has been rapidly recognized, the detailed nature of the mechanism of this reaction still remains in question. The cycloaddition has been formulated as a concerted electrocyclic process by Woodward and Hoffman.[19] This formulation has recently received support from Frontier orbital calculations,[20,21,22] which successfully predict the regioselectivity of the reaction. On the other hand, MINDO/3 calculations[23] indicate a highly unsymmetrical transition state in which the two new σ bonds are formed at two different "stages" of the reaction.[24] The dramatic rise in applications of this reaction to natural products synthesis, can be attributed in part to the development of a series of empirical rules which allow easy prediction of the

*For general references on the Diels-Alder reaction, see references 1-12.

structural outcome of the reaction. Furthermore, the observations that catalytic amount of Lewis acid can greatly enhance the rate,[25,26,27] as well as the stereo-[28] and regio-selectivity[29,30,31] of the reaction have widened the scope and potential applications tremendously.

Over the years, an understanding of the characteristic features of the Diels-Alder reaction has emerged. This has led to the development of a series of empirical rules which has greatly facilitated predictions of the structural outcome of this reaction. An important feature that has been recognized from the reaction is now embodied in the cis-principle which predicts that addition to the diene in the required cisoid conformation occurs from the same side at each end of the diene moiety and also that attack at both ends of the dienophilic double-bond occurs from the same face of the dienophile. It also predicts that the relative configurations of the substituents in the transition states (for example, **3a**, Scheme I) are preserved in the products. This can be illustrated by the reaction of trans, trans-1,4-diphenyl-1,3-butadiene (**1**) with maleic anhydride (**2**) to give stereospecifically the adduct **3**[11,32] (Scheme I). The cis-principle to which no violation has been observed to date, is classified by the Woodward-Hoffmann rules for pericyclic reactions[19] as a concerted $2\pi s+4\pi s$ cycloaddition reaction.

The endo-rule was originally formulated for additions

of cyclic dienes and dienophiles by Alder and Stein in 1937.[11,33] It predicts that of the two possible "sandwich-like" transition states (for example **5a** and **6a**, Scheme II), the more preferred would be that with the "maximum concentrations of double-bonds". Thus, reaction of 1,3-cyclopentadiene (**4**) with maleic anhydride (**2**) proceeds to give only the endo-adducts **5** and not the exo-adduct **6** (Scheme II). The preferred formation of the endo-adduct in the Diels-Alder reaction can be explained by a stabilization of the transition state (for example, **5a**) in which secondary orbital overlap can occur between the π system of the diene and the directing substituent of the dienophile. The term "exo" therefore refers to the addition via the transition state (for example, **6a**) in which no secondary orbital overlap can occur. These explanations for the endo-rule can equally be applied to acyclic cases. Thus, according to the endo-rule, trans,trans-2,4-hexadiene reacts with acrylic acid to give the endo-addition product **7** rather than the exo-addition product **8**.[34]

In the reactions between unsymmetrical dienes and dienophiles, regioisomeric adducts can, in principle, be formed. Usually, a regioisomer is preferentially obtained and such a bias in favor of one regioisomer is governed by a series of orientational rules which have greatly simplified prediction of the structural outcome of the reaction. The

ortho-rule will operate for the case of the reaction of a 1-substituted diene to give the adduct in which the C-1 substituent from the diene component is adjacent (ortho) to the substituent from the dienophile. Thus, the principal adduct from the reaction of trans-piperylene with acrolein is adduct **9** rather than the aldehyde **10**.

In the case of a 2-substituted diene, the structural outcome of the reaction is governed by the para-rule. It predicts that the substituent on C-2 of the diene will promote addition to give the adduct in which the two substituents are in a para-relationship. It was thus observed that reaction of isoprene with acrolein leads to the predominant formation of the adduct **11**.[1] The regioisomeric adduct **12** was obtained as a minor product.

If a 1,3-disubstituted diene is used, the ortho- and para-rules operate in a complementary fashion and will give the adduct obeying both rules. For example, reaction of trans-2-methyl-1,3-pentadiene with methyl acrylate gives **13** as the major adduct and **14** as the minor product.[1] However, out of the two competing ortho- and para-rules that can operate in the case of a 1,2-disubstituted diene, the ortho-rule will usually predict the course of the reaction. Thus, 1,2-dimethyl-1,3-butadiene reacts with acrylonitrile to yield adduct **15** as a major regioisomer and adduct **16** as a minor isomer.[1]

In the course of a study[21,22] of the regioselectivity

of the Diels-Alder reaction using Frontier orbital theory, Houk predicted[21] that, where substituents of both diene and dienophile are electron-donating, the favored product should have the substituents in a meta-orientation. This "meta-rule" has since been observed experimentally by Fleming.[35] Thus, the major product of addition of ethyl vinyl ether to the diene **17** was adduct **18**.[35]

The observations that Lewis acid catalysis produces large increases in the rate of the Diels-Alder reaction[25,26,27] have made available many adducts which had previously been obtained with difficulty (sealed tubes, high temperatures, etc.). Furthermore, it has been observed that such catalysis also has a profound effect on the regio- and stereo-selectivity of the addition so that the ortho-[31] and para-selectivity[29,30] of the addition as well as the endo-selectivity[28] are markedly increased.

In principle, the application of the Diels-Alder reaction to the synthesis of cis-1-octalones requires only a straightforward addition of a conjugated cyclohexenone to an appropriately substituted 1,3-butadiene. The cycloaddition offers a potentially direct and versatile approach to the decalin systems of a large number of sesquiterpenes such as the eremophilane (**19**), eudesmane (**20**) and cadinane (**21**) classes. Furthermore, the usually high stereo- and regio-selectivity of the reaction makes it an attractive method

for decalin synthesis. However, the thermal cycloaddition of dienes to cyclohexenones is notoriously recalcitrant. Early reports of low yields obtained and the drastic reaction conditions required for the addition appear to have discouraged continued investigations for the direct generation of octalones. For example, reaction of 1,3-butadiene with 2-cyclohexenone at 180-190°C for 3 days reportedly gave adduct **22** in only 11% yield.[36] Recently, it has however, been shown that Lewis acid could be applied to the addition of cyclohexenones to give synthetically useful yields of adducts. Kitahara and co-workers[37] reported on the aluminium chloride catalysed addition of several dienes to 2-methyl-2-cyclohexene-1-one while the aluminium chloride catalysed addition of 1,3-butadiene to a series of cycloalkenones and 2-methyl-cycloalkenones has been reported by Wenkert and collaborators.[38,39,40,41]

Liu and Browne have carried out an extensive study[42] of the Diels-Alder reactions of 4,4-dimethyl-2-cyclohexen-1-one (**23**) and its derivatives **24** and **25**. They have also observed improved yields by Lewis acid catalysis.[42] Furthermore, by the introduction of another electron-withdrawing group (for example, **25**), it was observed that the dienophilicity is considerably improved. This was reflected in the shorter reaction time used and the higher yields obtained for the adducts.[43] Also, the study indicates the potential of using

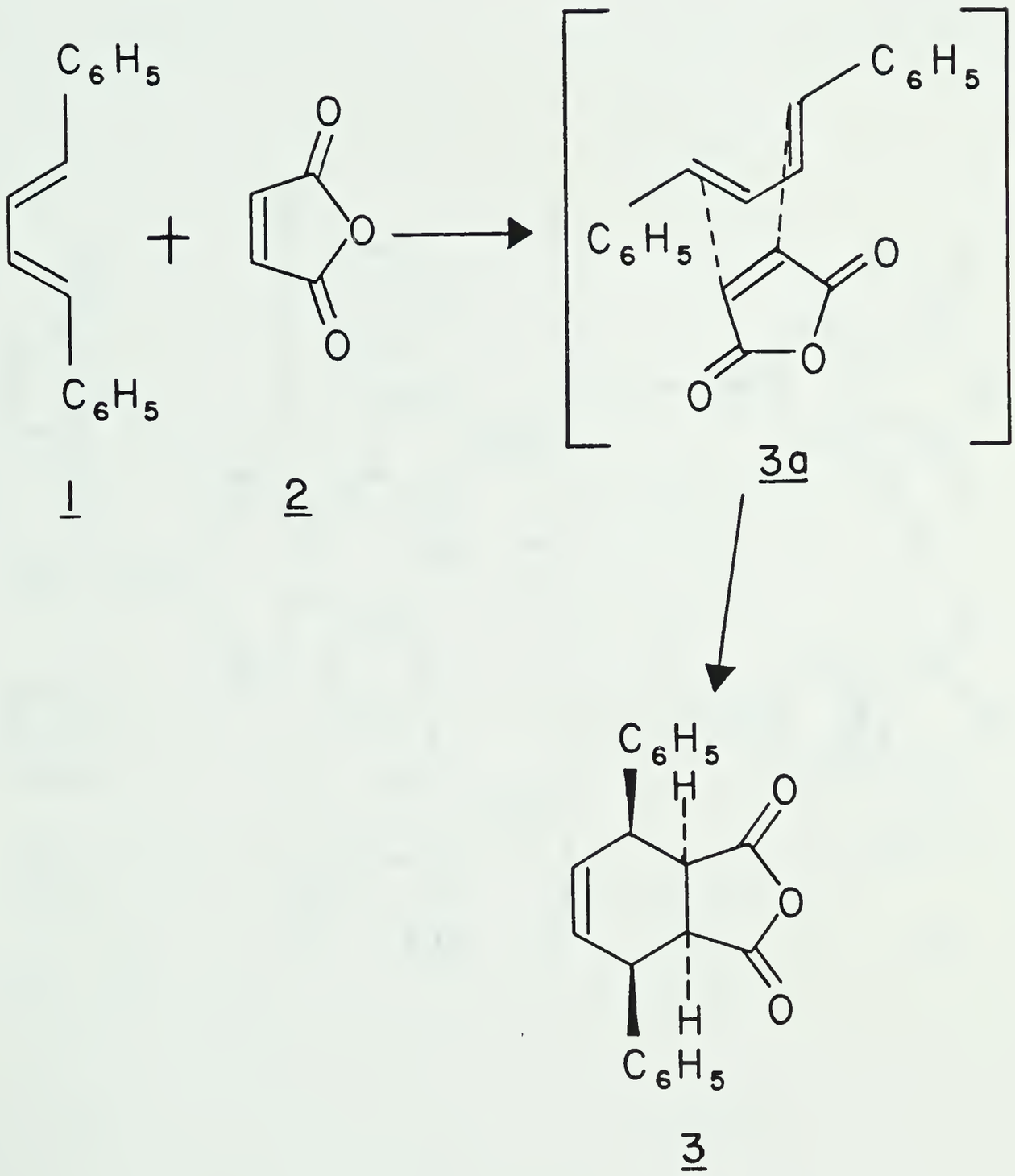
different Lewis acid catalysts to effect different regiochemical outcomes in the reaction of isoprene with the dienone **25.** Thus, addition of isoprene to **25** in ether at room temperature and under boron trifluoride etherate catalysis gave the adducts **26** and **27** in a ratio of 70:30. The formation of the abnormal anti-para adduct **26** as the major isomer has been rationalized by a steric effect.[42] On the other hand, by using stannic chloride as the catalyst, an 18:82 ratio of **26** to **27** was obtained. In this case, the normal para-adduct **27** which was obtained as the major product, was formed by a dominating electronic effect exerted by the bidentate stannic chloride on the keto-ester moiety of **25**.[42]. This finding has culminated in the successful syntheses of α- and β-himachalene by the use of adduct **27**.[44]

Although conjugated cyclohexenones having an additional electron-withdrawing group attached to the dienophilic double bond have been observed to display improved dienophilicity in Diels-Alder reactions, few studies of using such cyclohexenone derivatives have been reported. Compounds that were studied, included those that were substituted either at the α-[43,45,46] or the β-carbon[47,48,49] of the cyclohexenones. In the former case of α-substituted compounds only those that were geminally substituted by methyl groups at the γ-carbon, whereby the facile

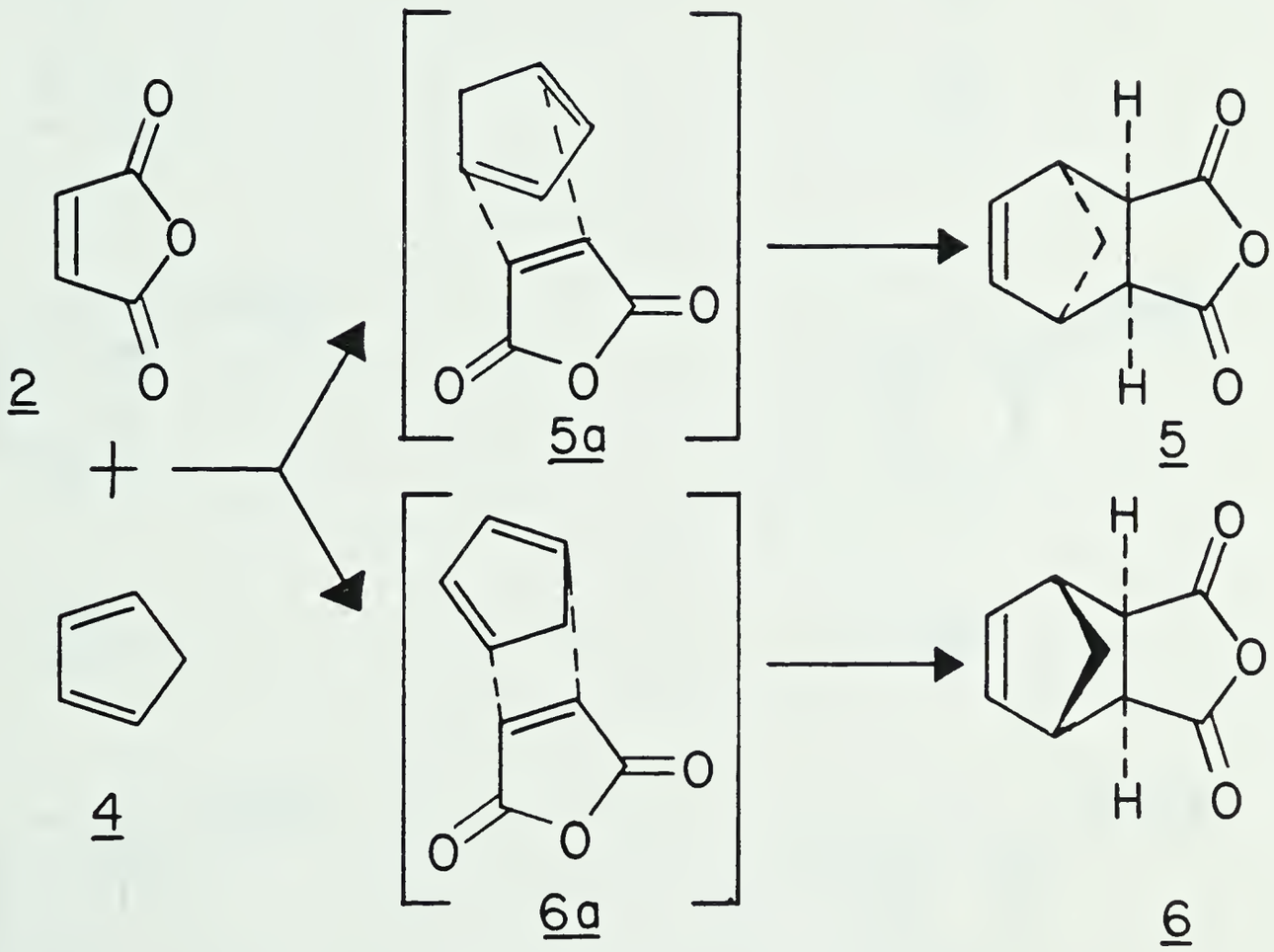
towards this center is blocked,[43,45,46] were explored. In spite of their broader synthetic utility, little is known about using enolizable analogs which have an electron-withdrawing α-substituent in Diels-Alder reactions.

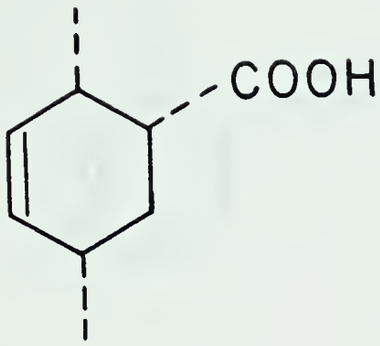
We have now examined the dienophilicity of 2-carbomethoxy-2-cyclohexen-1-one (**28**). The results as well as the structural aspects of this study will be discussed in this chapter of the thesis. Based on the results of this study, a total synthesis of petasitolone (**29**) was achieved and will be described in Chapter Two. The use of enone-ester **28** as a dienophile in a key Diels-Alder reaction for a synthetic study on the cardenolide, strophanthidin (**30**) is discussed in the final chapter of the thesis.

Scheme I



Scheme II





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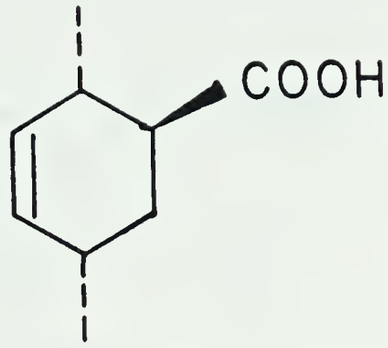

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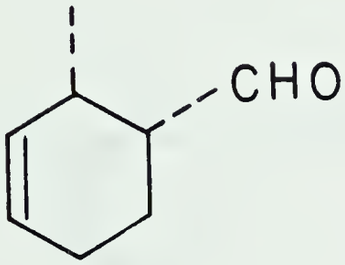

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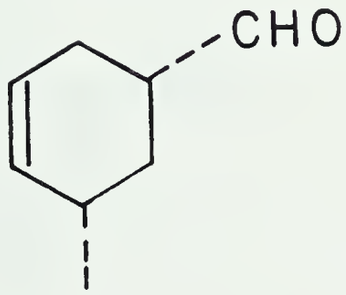

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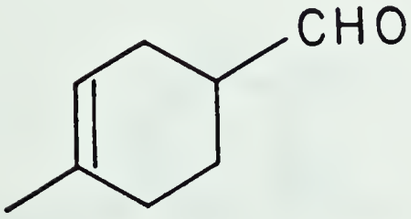

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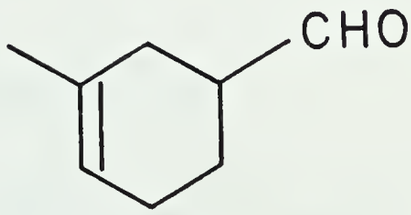

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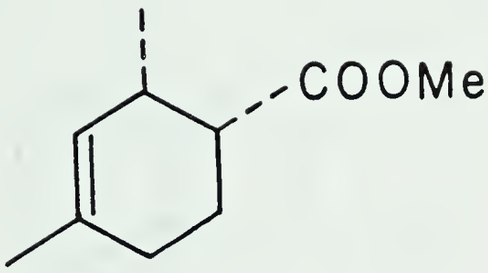

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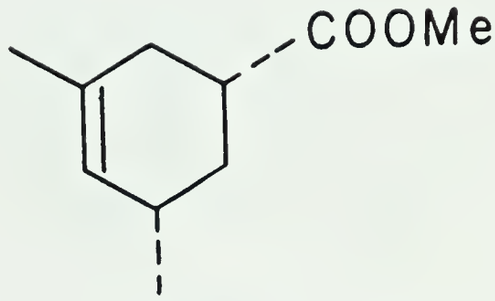

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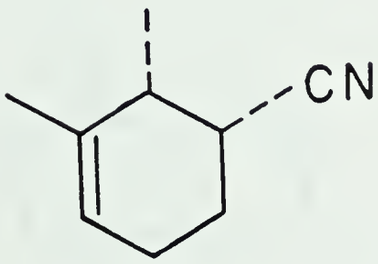

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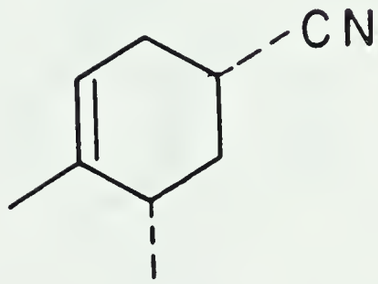

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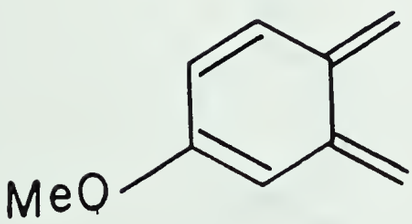

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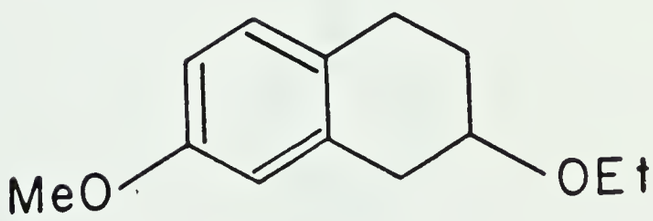

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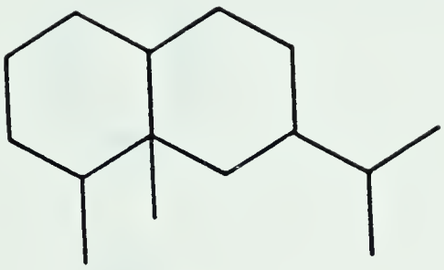

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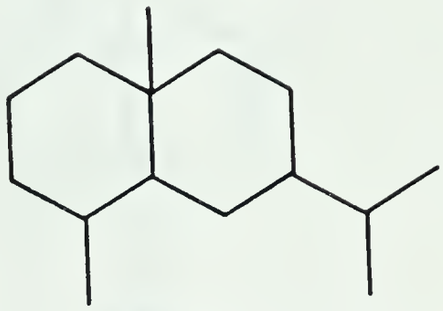

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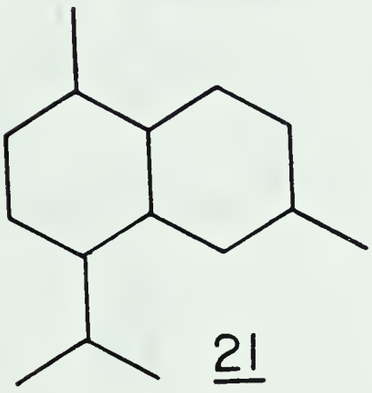

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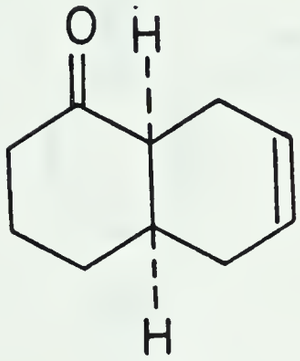

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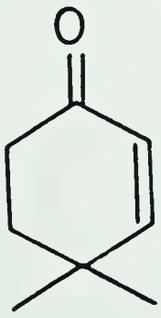

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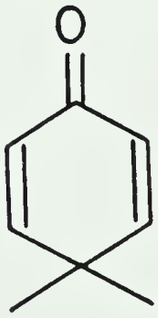

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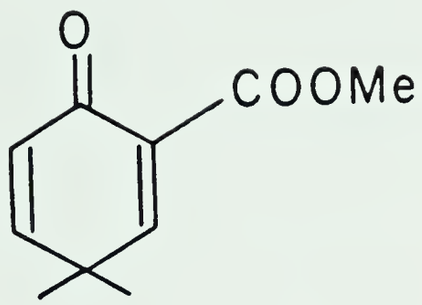

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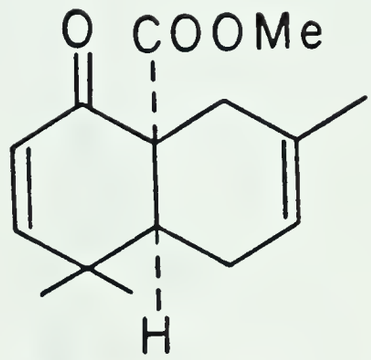

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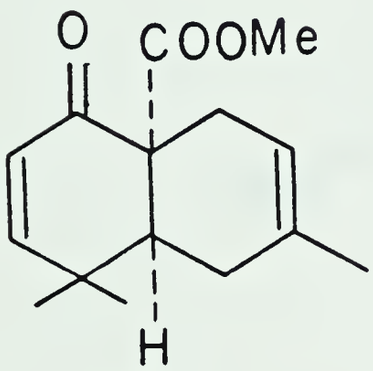

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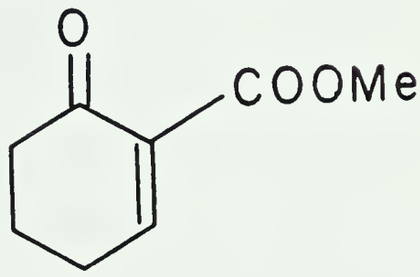

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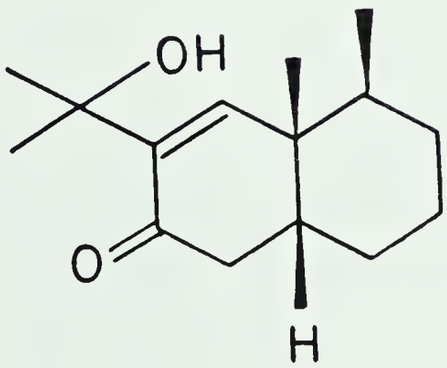

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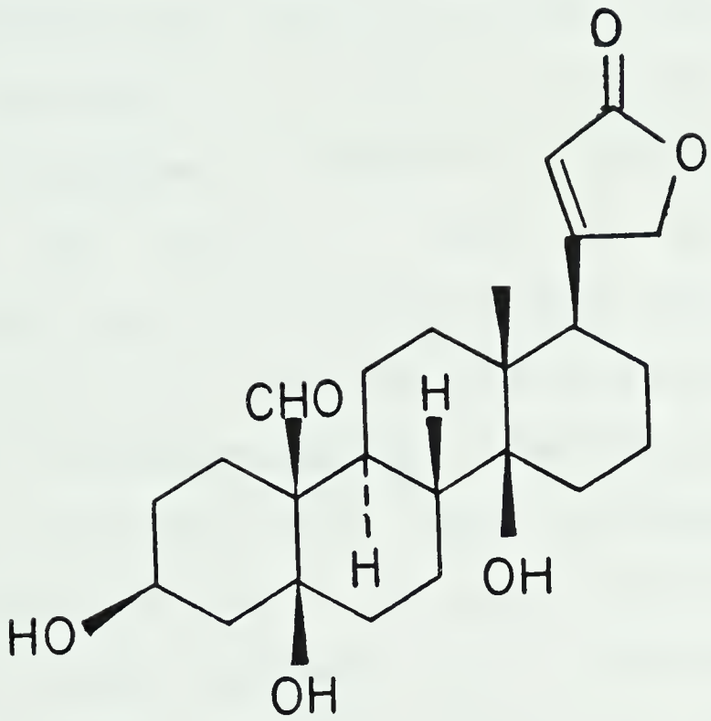


30

Results and Discussion

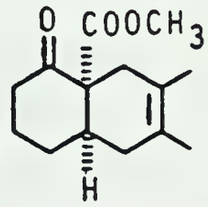
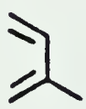
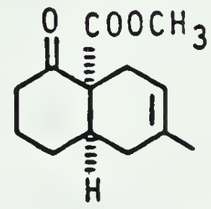
The effective preparation of 2-carbomethoxy-2-cyclohexen-1-one (**28**) has only been recently achieved when mild conditions for the carbon-carbon double-bond formation became available. It could be prepared according to the two-step procedure of Reich[50] or according to the method developed by Liotta.[51] Due to its simplicity and reproducibility, the latter procedure was preferred. This method involved the reaction of 2-carbomethoxycyclohexanone (**31**) with the phenylselenenyl chloride-pyridine complex[52] in methylene chloride at 0°C. After an aqueous acid extraction of the reaction mixture to remove pyridine, the resulting selenide **32** was oxidised with a solution of 30% aqueous hydrogen peroxide at 0°C, to give the required enone-ester **28** in quantitative yield.

The crude enone-ester **28** was found to enolize and decompose rapidly.* It was however shown to be spectroscopically pure by ^{1}Hmr analysis (for details, see Experimental). Attempts to purify by distillation led to a poorer yield of **28** and it was thus, more expedient to use the crude enone-ester **28** in the Diels-Alder reaction without

*To slow down decomposition and enolization, the crude oil is stored in a dry and clean flask which has been treated with NH_4OH before. Usually freshly prepared **28** is used.

further purification. A variety of conditions were initially used for the Diels-Alder reaction. It was found that thermal conditions were not effective in giving synthetically useful yields of adducts. For example, when freshly prepared enone-ester **28** was heated with 2,3-dimethyl-1,2-butadiene in benzene, only 6% yield of the adduct **33** was formed. Even with a more reactive diene, the yields of adducts were not significantly improved. Thus, reaction of enone-ester **28** with 2-trimethylsilyloxy-1,3-butadiene[53] carried out over a range of temperatures (20-120°C) gave at best 8% yield of the keto-ester **41** after hydrolysis. Preliminary study indicated that different Lewis acids could be used to catalyse the Diels-Alder reaction of enone-ester **28**. It was however observed that stannic chloride usually gave better yields of adducts (Table I). Subsequently, for futher exploration of the scope of the Diels-Alder reactions of enone-ester **28**, stannic chloride was chosen as the Lewis acid catalyst. The results of this study are summarized in Table II. The structures of adducts were established by spectroscopic analysis including ^{1}Hmr spin decoupling experiments as well as chemical studies or chemical correlation with known compounds. The ring junction stereochemistry of all the adducts followed from the <u>cis</u>-principle for which no

Table I. Diels-Alder Reactions of Enone-Ester **28** Using Different Lewis Acid Catalysts.[a]

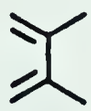
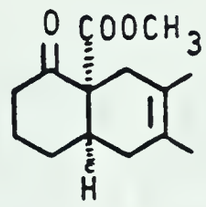
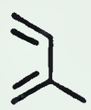
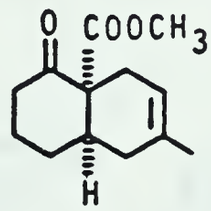
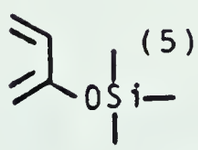
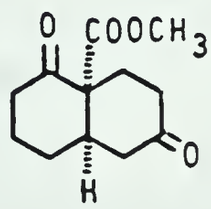
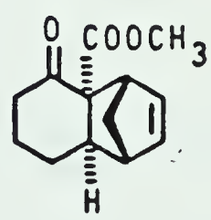
Entry	Diene[b]	Catalyst[b]	Time(h)	Product	% Yield[c]
1		BF_3OEt_2	3	 **33**	38
		$SnCl_4$	1.5	**33**	61
		$FeCl_3$	1.5	**33**	42
2		$SnCl_4$	1.5	 **34**	61
		$FeCl_3$	2	**34**	46

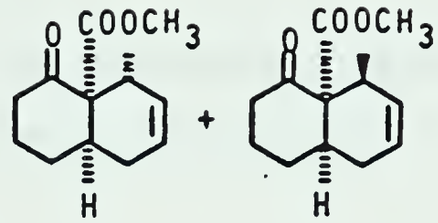
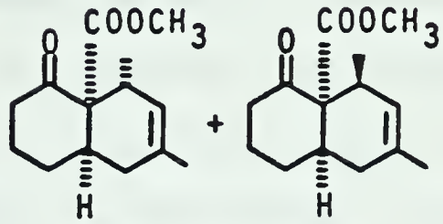
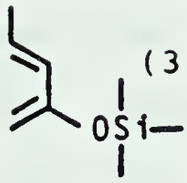
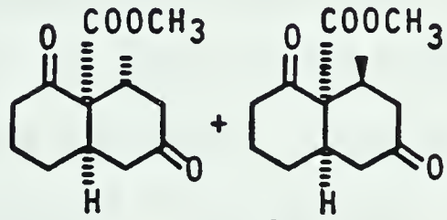
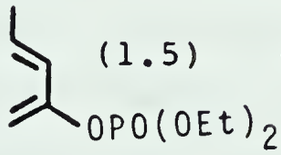
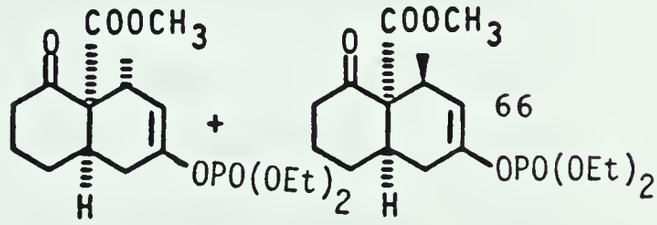
[a]All the reaction were done at 0°C using ether as the solvent.

[b]10 equivalent of dienes and 0.5 equivalent of Lewis acid catalysts were used.

[c]The yield of product was calculated based on 2-carbomethoxycyclohexanone.

Table II. Stannic Chloride Catalyzed Diels-Alder Reactions of Enone Ester **28**[a]

Entry	Diene (equiv.)	Temp (°C)	Time (h)[b]	Products (ratio)	% Yield[c]
1	 (10)	0	1.5	 **33**	61
2	 (10)	0	1.5	 **34**	61
3	 (5)	0	4	 **41**[d]	26
4	 (10)	-25	3	 **44**	29

5		(10)	0	5	 **46** (5:4) **47**	28
			-25	6	(5:3)	34
			-78	6	(5:3)	34
6		(3)	0	3	 **60** (2:1) **61**	34
			-35	3	(6:1)	34
			-78	3	(13:1)	37
7	 **62**	(3)	-30	5	 **64** (10:3)[d] **65**	45
8	 **63**	(1.5)	-30		 **68**(6:1)**69**	66

[a]Reactions were carried out in ether.
[b]Since the reactions could not be easily monitored, the cited time reflects only the period used to ensure its completion.
[c]The yield was calculated based on 2-carbomethoxycyclohexanone.
[d]Hydrolysis occurred during the work-up.

violations have been observed.* The structural aspects of each individual Diels-Alder adduct will be discussed in the following sections.

A. Addition to 2,3-dimethyl-1,3-butadiene.

When the reaction of enone-ester **28** with 2,3-dimethyl-1,3-butadiene was carried out in the presence of anhydrous stannic chloride in ether at 0°C, a crystalline adduct, m.p. 69-70°C, was obtained in 61% yield. A set of 14 lines in the ^{13}Cmr spectrum indicated the presence of a single isomer. The ir spectrum of the adduct showed absorptions at 1743 and 1717 cm^{-1} due to the presence of an ester and a ketone, respectively. A molecular ion peak at m/e 236.1414 in the mass spectrum gave the chemical formula as $C_{14}H_{20}O_3$. The ^{1}Hmr spectrum displayed a singlet at δ3.72 for a methyl ester and a broad singlet at δ1.64 integrating to six protons, was due to the presence of two vinylic methyl groups. The *cis* stereochemistry of the ring junction of the adduct was assigned on the basis of the *cis*-

*"Aside from the factors listed... (epimerization of adducts, migration of double-bond, reversibility of reaction)... which are independent of the reaction itself and its mechanism, no exceptions are known to the rule that the relative configuration of the starting materials is retained in the adduct; the reliability of the rule is one of the major factors in the importance of the Diels-Alder reaction in synthesis and in stereochemical studies."[8]

principle. Based on this and the preceding spectral data, structure **33** could be assigned to the adduct.

B. Addition to isoprene.

The reaction of an ethereal solution of enone-ester **28** with isoprene under stannic chloride catalysis proceeded smoothly and rapidly at 0°C to give an adduct in 61% yield. The ^{13}Cmr spectrum displayed a set of 13 lines indicating the presence of a single compound. The mass spectrum showed a molecular ion peak at m/e 222.1256 corresponding to the chemical formula $C_{13}H_{18}O_3$. The ir spectrum showed bands due to a saturated ester (1743 cm^{-1}) and a ketone (1714 cm^{-1}). Its ^{1}Hmr spectrum showed a multiplet at δ5.32 for the vinylic proton. A methyl ester signal appeared at δ3.73 as a singlet. If the Diels-Alder addition followed the normal *para*-rule, then, these spectral data suggested that the structure **34** could be assigned to the adduct.

However, it is known that the Diels-Alder reaction with a 2-substituted diene could lead to regioisomeric mixture of products and orientational reversal in violation of the *para*-rule has also been observed.[44] It was therefore possible that the addition of isoprene to enone-ester **28** could lead to the regioisomeric keto-ester **35**. To rule out

this possibility, a more rigorous proof of the regiochemistry was warranted. A conclusive proof of the regiochemistry of this adduct might be achieved by aromatization of the B-ring. Such a derivatization of the Diels-Alder adduct could lead to either the aryl-ketone **36** or the regioisomeric aryl-ketone **37**. Distinguishing these aryl-ketones should be possible by inspection of the ^{1}Hmr spectrum. The peri-effect[54] of the carbonyl on the proton (or substituent) at C-8 which is held in the deshielding zone of the carbonyl group, should cause the ^{1}Hmr signal of that proton (or substituent) to be shifted downfield significantly. For instance, the ^{1}Hmr spectrum of the known aryl-ketone **38**[42] (in deuterochloroform) was reported to show a doublet at δ7.95 with coupling constant of 8.0 Hz, due to the peri-proton at C-8 while the remaining aromatic protons appeared at δ7.20 as a broad singlet and at δ7.09 as a doublet of doublets. The other known regioisomeric aryl-ketone **39**[42] showed a singlet at δ7.90 due to the peri-proton at C-8 while the remaining aromatic protons appeared at δ7.37 and 7.27.

The aromatization of the Diels-Alder adduct **34** could be achieved by the removal of the angular methyl ester, followed by a dehydrogenation of the B-ring of the resulting ketone **40**. Thus, adduct **34** was treated with lithium iodide dihydrate[55] in refluxing 2,4,6-collidine to give an epimeric

mixture of ketones **40** in 40% yield. The mixture showed a molecular ion peak at m/e 164.1197 in the mass spectrum corresponding to the chemical formula $C_{11}H_{16}O$. The ir spectrum showed a band at 1714 cm^{-1} corresponding to a ketone. The ^{1}Hmr spectrum showed a multiplet at δ5.37 due to the vinylic proton and a methyl singlet appeared at δ1.60. These spectral data are consistent with the assignment of structure **40** to the decarbomethoxylated product.

Treatment of the mixture of epimeric ketones **40** with N-bromosuccinimide in refluxing carbon tetrachloride[45,56] gave a product in 64% yield. Its ir spectrum showed a signal due to an aryl-ketone (1682 cm^{-1}). The mass spectrum showed a molecular ion peak at m/e 160.0879 corresponding to the chemical formula $C_{11}H_{12}O$. The ^{1}Hmr spectrum displayed signals at δ2.11, 2.61 and 2.90 for the six methylene protons. A methyl singlet appeared at δ2.37, characteristic of an aryl-methyl group. Furthermore, three signals, assignable to the aromatic protons, appeared at δ7.04 as a singlet, 7.10 and 7.92 as doublets. These splitting patterns displayed by the aromatic protons, especially the doublet at δ7.92 for the peri-deshielded proton at C-8, could only be due to the aryl-ketone **36**. The other regioisomeric aryl-ketone **37** would be expected to show a singlet for the peri-deshielded proton at C-8. Thus, the

Diels-Alder adduct from the addition of isoprene and enone-ester **28** must have the regiochemistry as depicted in structure **34**.

C. Addition to 2-trimethylsilyloxy-1,3-butadiene.

The addition of 2-trimethylsilyloxy-1,3-butadiene[53] to the enone-ester **28**, under stannic chloride, proceeded at 0°C to give an adduct which was recrystallized as white crystals (m.p. 87-88°C). A set of 12 lines in the ^{13}Cmr spectrum indicated that the isolated product was a single compound. The ir spectrum showed absorptions due to an ester (1743 cm^{-1}) and a ketone (1715 cm^{-1}). In the mass spectrum, a molecular ion peak at m/e 224.1049 indicated the chemical formula of $C_{12}H_{16}O_4$. The ^{1}Hmr spectrum showed a methyl ester singlet at δ3.75 and the absence of olefinic and trimethylsilyloxy protons. The remaining signals that appeared from δ3.04 to 1.54, were characteristic of methylene and methine protons. If the Diels-Alder reaction followed the normal *para*-rule, then these spectral data are in agreement with the structure **41** for the adduct. The *cis* relative stereochemistry of the ring junction was again assigned based on the *cis*-principle. Apparently, hydrolysis of the silyl enol ether moiety of the initially formed adduct **42** occurred during the work-up of the reaction

mixture.

Evidence in support of the regiochemical assignment for the adduct **41** was obtained from a closer examination of the high field ^{1}Hmr spectrum (400 MHz). A one-proton signal appeared at δ3.10 with three coupling constants of 7.0, 7.0 and 3.0 Hz. This signal was assigned to the methine proton at the ring junction. It was observed that this signal was coupled to a doublet at δ2.21 (J = 7.0 Hz).* This latter signal which integrated for two protons in the ^{1}Hmr spectrum, was assigned to the methylene protons at C-5.** Clearly, these data in the ^{1}Hmr spectrum are consistent with the structure **41** for the Diels-Alder adduct. The regioisomeric adduct **43** would be expected to show no vicinal coupling for the methylene protons at C-8. It should show a doublet for each proton (each with geminal coupling constant), or if magnetically equivalent, should show a singlet.

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*This coupling was confirmed by irradiation of signal at δ3.10 which led to a singlet for the signal at δ2.21. Conversely, a doublet of doublets was observed at δ3.10 on irradiation of the signal at δ2.21.

**Incidentally, these two methylene protons have the same chemical shift. However, when the nmr spectrum was run in deuterobenzene, these two protons showed different chemical shifts at δ1.91 and 1.80. The signal at δ1.91 showed coupling constants of 14.5, 5.5 and 1.0 Hz while the signal at δ1.80 gave coupling constants of 14.5, 8.5 and 1.5 Hz.

D. Addition to cyclopentadiene.

The addition of cyclopentadiene to enone-ester **28** under stannic chloride catalysis proceeded at -25°C, to give an adduct in 29% yield. Recrystallization of this adduct with a mixture of ether and petroleum ether gave white crystals of pure adduct (m.p. 91-93°C). The ^{13}Cmr spectrum showed a set of 13 lines indicating the presence of a single isomer. The mass spectrum showed a molecular ion peak at m/e 220.1098 corresponding to the chemical formula $C_{13}H_{16}O_3$. The ir spectrum showed bands due to a saturated ester (1730 cm^{-1}) and a ketone (1709 cm^{-1}), as well as a band at 705 cm^{-1} suggesting a cis disubstituted double-bond. The ^{1}Hmr spectrum showed the presence of two vinylic protons at δ6.31 and 6.00, each appearing as a doublet of doublets. A methyl signal appeared as a singlet at δ3.67.

Preliminary analysis of the spectral data indicated that the structure of the adduct was either **44** or **45**. An examination of molecular models revealed that the keto-ester **44** would have the conformation **44a** in which a long range w-coupling between the proton on C-4a and one of the protons on C-9 (Hx) would be expected in the ^{1}Hmr spectrum. On the other hand, in **45a** no such w-coupling would be expected.

Decoupling experiments of all isolable signals in the ^{1}Hmr spectrum have led to the assignments of all the protons

on the bicyclo [2.2.1] ring system of the adduct. The signal for the C-4a proton appeared at δ2.52, with coupling constants of 12, 7.0 and 2.0 Hz, while the signal at δ1.42 was due to the Hx proton on C-9. This latter signal had coupling constants of 9.0, 2.0 and 1.0 Hz. Irradiation of the signal at δ1.42 led to simplification of the signal at δ2.52 to a doublet of doublets with coupling constants of 12 and 7.0 Hz. Conversely, irradiation of signal at δ2.52 led to the disappearance of the 2.0 Hz coupling constant for the signal at δ1.42. These ^{1}Hmr data supported the assignment of structure **44** to the adduct.

E. Addition of trans-piperylene

When an ethereal solution of enone-ester **28** was reacted with trans-piperylene at 0°C and under stannic chloride catalysis, a 5:4 mixture of two inseparable adducts was obtained in 28% yield. The ir spectrum of this mixture showed absorptions at 1743 and 1717 cm^{-1}, characteristic of the presence of an ester and a ketone, respectively. The mass spectrum showed a molecular ion peak at m/e 222.1256, corresponding to the chemical formula $C_{13}H_{18}O_3$. The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 5:4. The major set showed a multiplet at δ5.32 due to the presence of two vinylic protons. A methyl singlet appeared

at δ3.72 and a methyl doublet appeared at δ0.83. The minor set showed a multiplet at δ5.63 due to two vinylic protons. Methyl signals appeared at δ3.78 as a singlet and at δ1.17 as a doublet.

If the Diels-Alder reaction obeyed the normal ortho-rule, then the structures of the adducts could be tentatively assigned to the epimeric keto-esters **46** and **47**. Abnormal additions would lead to the regioisomeric keto-esters **48**. To conclusively determine the regiochemistry, the 5:4 mixture of Diels-Alder adducts was converted to the corresponding aryl-ketone derivative. As discussed in the preceeding section (Section B), differentiation of the resulting aryl-ketone, either **49** or **50**, should be possible by ^{1}Hmr analysis. The aryl-ketone **49** should show a downfield singlet for the peri-deshielded aryl methyl while **50** should show a downfield doublet for the peri-deshielded aromatic proton.

Decarbomethoxylation of the mixture of Diels-Alder adducts was achieved by treatment with lithium iodide dihydrate in refluxing 2,4,6-collidine. After purification by flash chromatography, a mixture of three ketones was obtained. The ir spectrum of the mixture showed a ketone carbonyl absorption at 1712 cm^{-1}. In the mass spectrum, a molecular ion peak at m/e 164.1198 ($C_{11}H_{16}O$), appearing as a base peak, was observed. The ^{1}Hmr spectrum showed three

sets of doublets at δ1.00, 0.99 and 0.98. A complex multiplet at δ5.56 was due to the two vinylic protons of the mixture of ketones. These spectral data are in agreement with either the mixture of ketones **51** and/or the regioisomeric ketones **52**.

The mixture of ketones was dehydrogenated with N-bromosuccinimide in refluxing carbon tetrachloride. After purification, a single aryl-ketone was obtained in 58% yield. Its ir spectrum showed a band at 1690 cm^{-1}, characteristic of an aromatic ketone. A molecular ion peak at m/e 160.0871 in the mass spectrum showed aromatic signals at δ7.30 (two protons) and 7.05. The aryl-methyl signal appeared at δ2.64 as a singlet. The absence of any low field signal at a value above δ7.30 as well as the presence of an aryl-methyl signal at a chemical shift lower than normal were in agreement with the assignment of structure **49** for the aryl-ketone. Thus, the Diels-Alder adducts must possess the regiochemistry as depicted by structures **46** and **47**, epimeric to each other at the C-8 center.

It remained to determine which epimer of the two was the major adduct of addition. This determination was made by a chemical correlation of the major adduct to a known compound. The mixture of adducts was hydrogenated with Raney-nickel (grade W-2) in ethyl acetate at room temperature to give the chromatographically separable keto-

esters **53** and **54** in 84% yield. The structure of the major keto-ester **53** was confirmed by its conversion to the known ketone **55** by a four-step sequence which will be described in chapter two of this thesis. This correlation conclusively established the structure of the major Diels-Alder adduct as **46**. Since the minor adduct has to be epimeric at C-8, it thus must have the structure **47**.

At this stage it is useful to introduce several features of the ^{1}Hmr spectrum of the adducts **46** and **47** which can be used in determining the C-8 stereochemistry of other adducts in this series. It was observed that the secondary methyl group of **47** appeared at δ1.17 and was strongly deshielded relative to that of the secondary methyl of **46** (δ0.83). Conversely, the allylic methine proton at C-8 of **46** appeared at δ2.92 and was strongly deshielded relative to that of the allylic methine proton at C-8 of **47** (δ2.49).* These observations can be attributed to a deshielding of the C-8 proton or methyl which is <u>trans</u> to the angular carbomethoxyl group in the adduct, by the ketone carbonyl group. A rational for this observed effect could be obtained from a consideration of the conformations of these adducts. Adduct **47** would have the conformations **47a** and **47b**

*These assignments for the allylic methine protons (δ2.92 and 2.49) were confirmed by the observations of significant sharpening of these signals upon irradiation of the adjacent protons of the methyl group (δ0.83 and 1.17).

(Scheme III) in which **47b** would have the C-8 methyl in the deshielding zone of the ketone carbonyl. Adduct **46** would have the conformations **46a** and **46b** in which **46b** would have the C-8 proton in the deshielding zone of the ketone carbonyl.

These results in the ^{1}Hmr spectrum were consistently observed in similar decalin derivatives as well. For instance, in the ketone **57**, the secondary methyl group appeared at δ1.11 deshielded relative to the corresponding methyl group of **56** (δ0.77). Similarly, in ketone **58**, the allylic methine proton on C-8 showed a signal at δ3.06, strongly deshielded relative to the C-8 proton of **59** (δ2.34), while the C-8 methyl of **59** appeared at δ1.38, shifted downfield relative to that of the corresponding methyl of **58** (δ1.04).

F. Addition to *trans*-2-methyl-1,3-pentadiene

The Diels-Alder addition of *trans*-2-methyl-1,3-pentadiene to enone-ester **28** under stannic chloride catalysis at 0°C gave an inseparable mixture of adducts in 34% yield. The ir spectrum showed absorptions at 1740 and 1719 cm^{-1}, due to the presence of an ester and a ketone respectively. A molecular ion peak at m/e 236.1413 in the mass spectrum indicated the chemical formula as $C_{14}H_{20}O_3$.

The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 2:1. One set, due to the major adduct, consisted of methyl signals at δ3.63 as a singlet and at δ0.73 as a doublet, as well as a vinylic proton signal at δ5.25 as a multiplet. The other set, due to the minor adduct, showed a methyl singlet at δ3.70 and a methyl doublet at δ1.08, as well as a multiplet at δ5.15 due to a vinylic proton.

Attempts to determine the regiochemistry of the Diels-Alder adducts were not successful. Previous observations indicated that the ortho- and para-rules (Table II, Entries 2, 3 and 5) were consistently followed throughout the series. It was therefore expected that the ortho- and para-rules would operate in a complementary fashion in this case to give the electronically favored adducts **60** and **61**. This assignment was also supported by the results of the additions of the 1,3-disubstituted dienes **62** and **63** to enone-ester **28**. In these cases, the additions gave the adducts (**64** and **65**; **68** and **69**), obeying the normal ortho- and para-rules (see following sections). These results could be taken as an indirect evidence that the addition of trans-2-methyl-1,3-pentadiene to **28** would follow the normal ortho- and para-rules to give the C-8 epimeric keto-esters **60** and **61** (vide infra).

It remained to determine which was formed as the major isomer as well as which was the minor isomer. As discussed

in Section F, the ^{1}Hmr spectral data could be used to determine the C-8 stereochemistry of the keto-esters **46** and **47**. The determination could be made on the basis of the deshielding of the C-8 proton of **46** and the deshielding of the C-8 methyl of **47** by the ketone carbonyl. Thus, in an analogous manner, the C-8 proton of **60** should be deshielded relative to that of **61**. Conversely, the C-8 methyl of **61** should be deshielded relative to that of **60**. In the ^{1}Hmr spectrum of the 2:1 mixture of epimers, the allylic methine proton at C-8 of the major adduct appeared at δ2.83 strongly deshielded relative to the C-8 proton of the minor adduct (δ2.40),* while the C-8 methyl of the minor adduct appeared at δ1.08, deshielded relative to the C-8 methyl of the major adduct (δ0.73). These data are in agreement with the assignment of the keto-ester **60** to the major adduct and the C-8 epimeric keto-ester **61** to the minor adduct.

The stereoselectivity in favor of the major keto-ester **60** as well as the yield was found to be improved by the use of a lower reaction temperature. At -30°C, it was observed that enone-ester **28** reacted with trans-2-methyl-1,3-pentadiene under stannic chloride catalysis to give a 6:1 mixture (compared to a 2:1 mixture at 0°C) of Diels-Alder

*The assignments for the allylic methine protons at C-8 (δ2.83 and 2.40) were confirmed by the observations of significant sharpening of the signals upon irradiations of the adjacent protons of the methyl groups (δ0.73 and 1.08).

adducts, in favor of **60** in 37% yield. To improve this stereoselectivity and the yield further, an even lower reaction temperature was employed. Thus, at -78°C, the Diels-Alder reaction proceeded to give an excellent 13:1 stereoselectivity in favor of **60**. However, the yield of adducts obtained was again 37%.

G. Addition to trans-2-trimethylsilyloxy-1,3-pentadiene (**62**)

The addition of trans-2-trimethylsilyloxy-1,3-pentadiene (**62**)[57] to enone-ester **28** proceeded at -30°C under stannic chloride catalysis to give an inseparable mixture of two adducts. The ir spectrum of the mixture showed absorptions at 1740 and 1714 cm^{-1} due to the presence of an ester and a ketone, respectively. A molecular ion peak at m/e 238.1205, appearing as a base peak in the mass spectrum corresponded to the chemical formula $C_{13}H_{18}O_4$. The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 3.3:1. The major set showed a methyl singlet at δ3.73 and a methyl doublet at δ0.90. The minor set showed a methyl singlet at δ3.82 and a methyl doublet at δ1.15. Preliminary analysis of these spectral data suggested that the structures of the adducts could either be the epimeric

diketones **64** and **65** and/or the regioisomeric diketones **66**.*

It was conclusively established that the Diels-Alder adducts must be the C-8 epimeric diketones **64** and **65** as follows. Treatment of the mixture of adducts with a solution of 5 equivalents of 1,2-ethanedithiol and 1 equivalent of boron trifluoride etherate in methylene chloride at 0°C for 30 min, furnished the thioketals **67** (for spectral data, see Experimental). Desulfurization of the thioketals **67** was achieved with Raney-nickel (grade W-2) in refluxing ethanol. After chromatographic separation, two products in a ratio of ~3:1 in a combined yield of 64% was obtained. The major product was found to be identical in ^{1}Hmr and ir spectra to the saturated keto-ester **53** obtained previously (see Section E). Similarly, the minor product was identical in spectral data (^{1}Hmr and ir) to the keto-ester **54** obtained previously (see Section E). This transformation just discussed unambiguously established the structures of the Diels-Alder adducts to be the epimeric diketones **64** and **65**, and that the former diketone **64** was formed as the major product of addition.

*As observed in Section C, hydrolysis of the labile silylenol ether moiety of the initially formed Diels-Alder adducts occurred during the work-up.

H. Addition to diethyl (trans-1,3-pentadien-2-yl)phosphate (**63**).

Under stannic chloride catalysis, an ethereal solution of enone-ester **28** reacted with diethyl (trans-1,3-pentadien-2-yl)phosphate (**63**) at -30°C to give a 6:1 mixture of adducts in 66% yield. The mixture showed ir absorptions at 1750 and 1720 cm^{-1} as well as a molecular ion peak at m/e 374.1495 ($C_{17}H_{27}O_7P$). The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 6:1. The major set of signals showed a multiplet at δ5.46 due to a single proton. A methyl ester singlet appeared at δ3.77 and a secondary methyl doublet appeared at δ0.91. Two multiplets appearing at δ4.16 and 1.40 were assigned to the ethyl protons of the phosphate group. The minor set showed a vinylic proton at δ5.33. The methyl signals appeared at δ3.81 as a singlet and at δ1.20 as a doublet. These spectral data indicated that the mixture of adducts could either be the epimeric enol-phosphate **68** and **69** and/or the regioisomeric enol-phosphates **70**.

The structures of the Diels-Alder adducts were unambiguously established to be the epimeric enol-phosphates **68** and **69** again by their transformation to the chromatographically separable keto-esters **53** and **54**, respectively. This conversion was easily achieved by the

hydrogenation of the mixture of adducts using platinum oxide as the catalyst.[58,59] In this way the double-bond as well as the phosphate group were reduced and a 6:1 ratio of **53** and **54** were isolated in 87% combined yield. The keto-esters **53** and **54** were each found to be identical in ^{1}Hmr and ir spectra, as well as silica gel thin-layer chromatographic behaviour to the keto-esters **53** and **54**, respectively, obtained in Section E (vide supra). It was thus established that the Diels-Alder addition of diene **63** to enone-ester **28** gave the epimeric enol-phosphate **68** and **69** in a ratio of 6:1.

When the reaction was carried out at -78°C, a similar stereoselectivity of 6:1 in favor of **68** was observed. However, the yield of adducts isolated was lower (45%). The use of methylene chloride as the solvent did not lead to any improvement in the results. For example, when the addition was done at -30°C in methylene chloride, a 6:1 ratio of **68** to **69** was again obtained and the yield was lower (50%).

I. endo-Selectivities of the additions

A detailed discussion of the endo-selectivities of the Diels-Alder reactions is warranted. It can be seen that enone-ester **28** has two dienophilic components; namely the α β-unsaturated ketone as well as the α,β-unsaturated ester moieties. Ordinarily, it would be unnecessary to

distinguish these two moieties except in cases where the endo-rule comes into effect. endo-Addition to the enone moiety of **28** would give a product different from that of endo-addition to the α,β-unsaturated ester moiety. The factor(s) determining which dienophilic moiety would dominate the reaction pathway is expected to be a function of which one would offer the most effective secondary orbital overlap with the diene. It was observed that the additions of 1-substituted dienes (Table II, Entries 4, 5, 6, 7 and 8) to enone-ester **28** appeared to proceed predominantly by secondary overlap with the ester group (transition state **71**) rather than with the ketone carbonyl (transition state **72**). The bias in favor of transition state **71** may be of electronic and steric origins.

The electronic effect exerted by the stannic chloride in complexing more effectively with the ester group of the enone-ester **28**, would favor the addition via transition state **71** to give the various major adducts (**44**, **46**, **60**, **64** and **68**). However, it would be difficult to ascertain this preferred complexation of the ester group by stannic chloride.

On the other hand, the addition via transition state **72** would encounter some steric interaction between the diene and the non-reacting centers of the cyclohexenone ring of the dienophile. The presence of the steric effect was

further substantiated by the use of a more bulky substituent at the C-3 position of the 1-substituted dienes which led predominantly to the adducts resulting from addition *via* transition state **71**.

The formation of two C-8 epimeric adducts **46** and **47** in a ratio of 5:4 by addition of *trans*-piperylene to **28** at 0°C clearly was the result of addition *via* two different transition states. Keto-ester **46** would be the result of addition *via* transition state **71a** while keto-ester **47** resulted from addition *via* transition state **72a**. The preferential formation of the adduct **46** is partly attributed to a destabilization of transition state **72a** by steric interaction between the diene and the non-reacting centers of the cyclohexenone ring of the dienophile.* Addition *via* transition state **71a** would not encounter such a steric interaction.

This steric effect was observed to be larger for the addition of *trans*-2-methyl-1,3-pentadiene. In this case, a larger product ratio (**60**:**61** = 2:1) was observed in favor of the addition *endo* to ester *via* transition state **71b** to give the adduct **60**. Clearly, in the addition *via* the competing transition state **72b**, a greater steric interaction would be

*A similar explanation has been offered to account for the relatively poor dienophilicity of cyclohexenones[8] and also to account for an orientational reversal in violation of the *para*-rule in the Diels-Alder reaction.[42]

encountered between the more bulky diene and the non-reacting centers of the ring moiety of the dienophile. This greater steric interaction has allowed the transition state **71b** to compete more effectively.

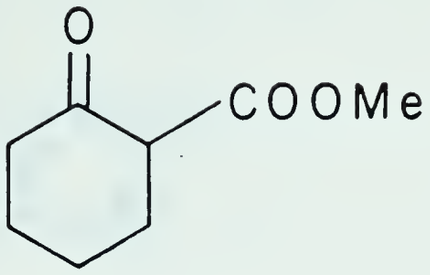
The cases of trans-2-trimethylsilyloxy-1,3-pentadiene (**62**) and diethyl trans-1,3-pentadien-2-yl phosphate (**63**) again showed very good stereoselectivities in favor of the adducts (**64** and **68**) resulting from additions of dienes endo to the ester group of enone-ester **28** (transition states **71c** and **71d**).

The addition of cyclopentadiene is also noteworthy. Its addition to enone-ester **28** gave only the adduct **44**, arising solely from endo addition to the ester group of **28**. Construction of molecular models for the transition states revealed that in **74**, a severe steric interaction would be encountered between the C-2 proton as well as the C-3 proton of the diene and the non-reacting centers of the cyclohexenone ring of the dienophile. On the other hand, in **73**, the methylene protons on C-5 of cyclopentadiene would be nearer the center of the cyclohexenone ring than closer to the non-reacting centers of the ring and would thus experience less steric interaction.

By the use of a lower reaction temperature, it would be expected that the stereoselectivity in favor of the endo to ester addition would be greater. This expectation was

indeed found to be true. For instance, for the case of trans-2-methyl-1,3-pentadiene, the stereoselectivity improved to 6:1 (compared to 2:1 at 0°C) in favor of adduct **60** when -30°C was employed. This stereoselectivity was improved even further at -78°C. A product ratio of 13:1 in favor of the "endo to ester" adduct **60** was obtained.

In conclusion, the development of enone-ester **28** as a dienophile makes available a new method for the rapid construction of angularly substituted cis-decalin derivatives. Furthermore, the angular carbomethoxyl group of the resulting cis-decalin derivatives can either be removed or used as a reactive site for further elaboration of the adducts. It is also worth mentioning that the stereochemical outcome of the additions of 1-substituted dienes to **28** is in contrast to that observed for the Lewis acid catalysed Diels-Alder reaction involving 2-cyclohexenone and 2-methyl-2-cyclohexenone. Hence, the two processes are complementary in stereochemical control.



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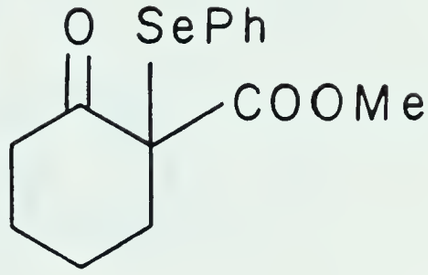

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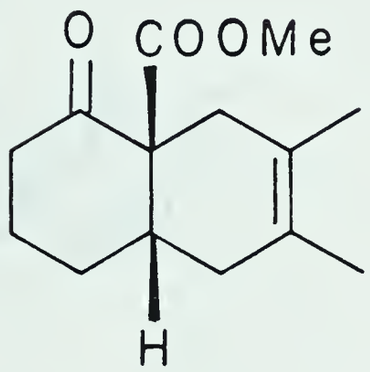

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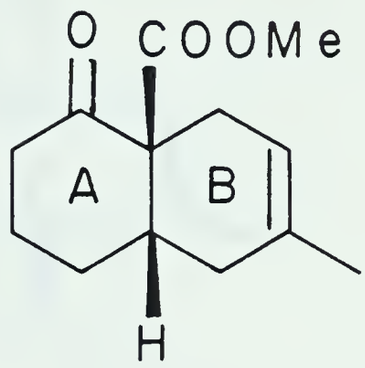

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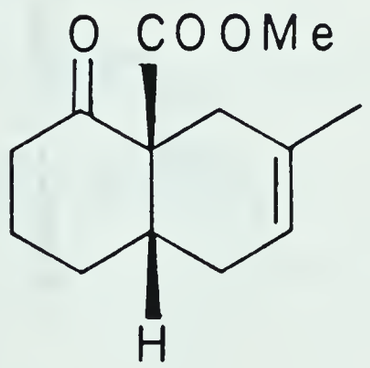

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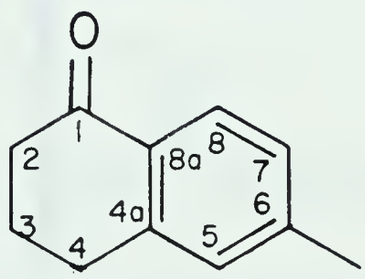

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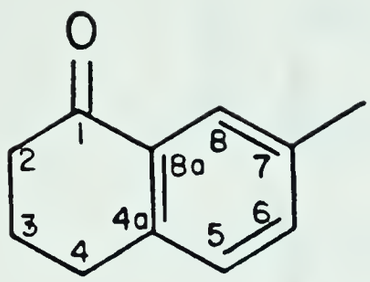

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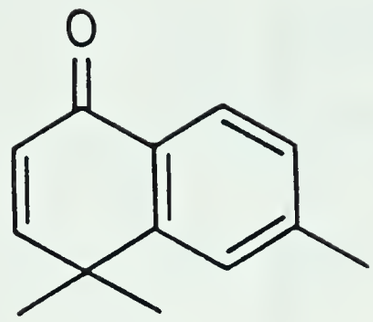

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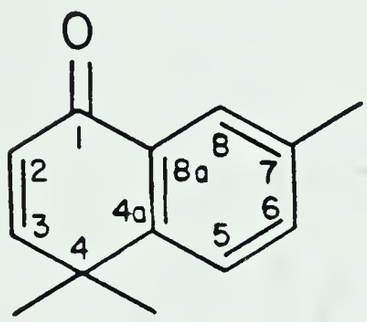

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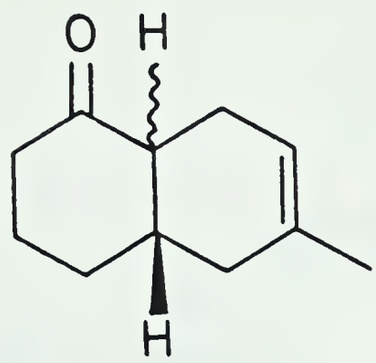

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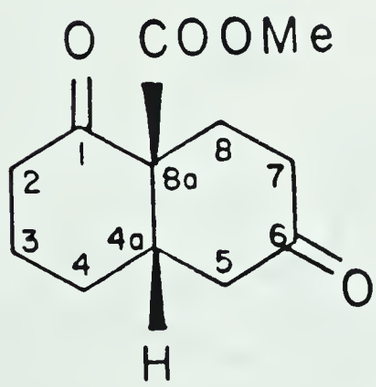

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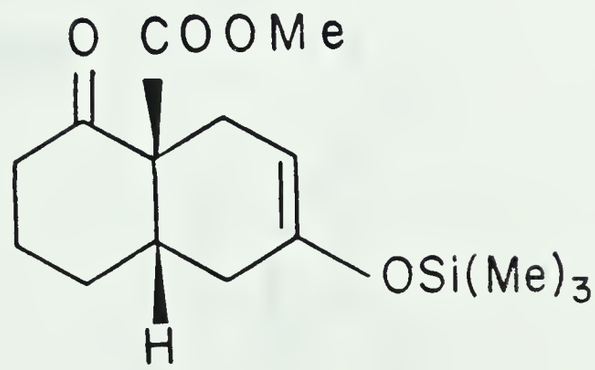

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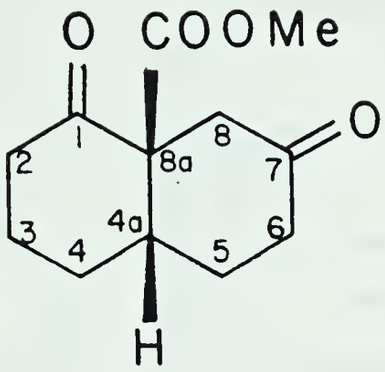

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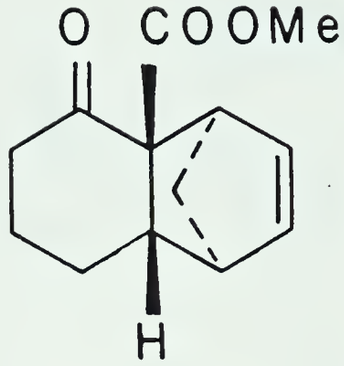

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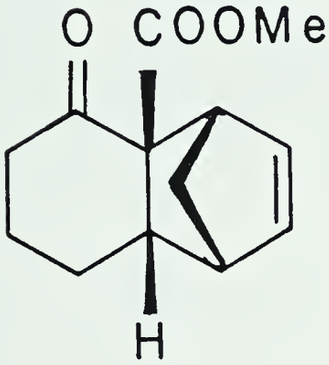

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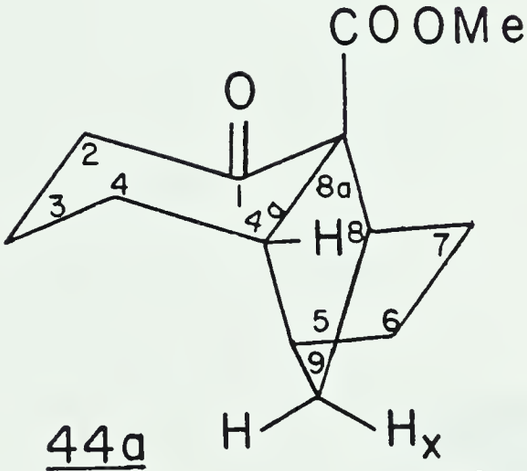

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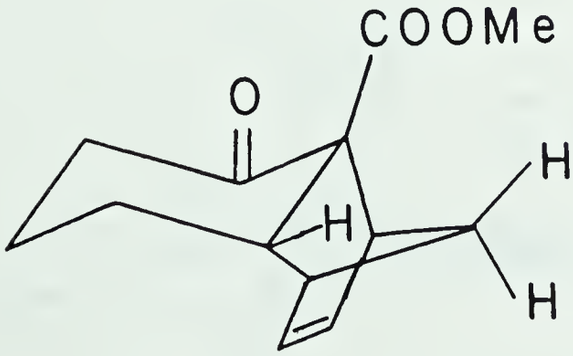

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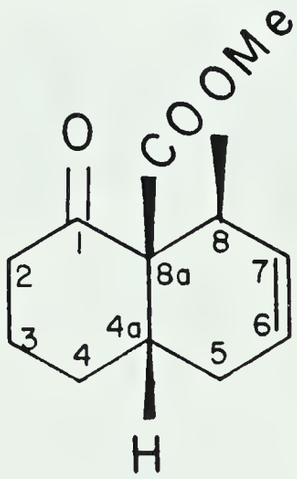

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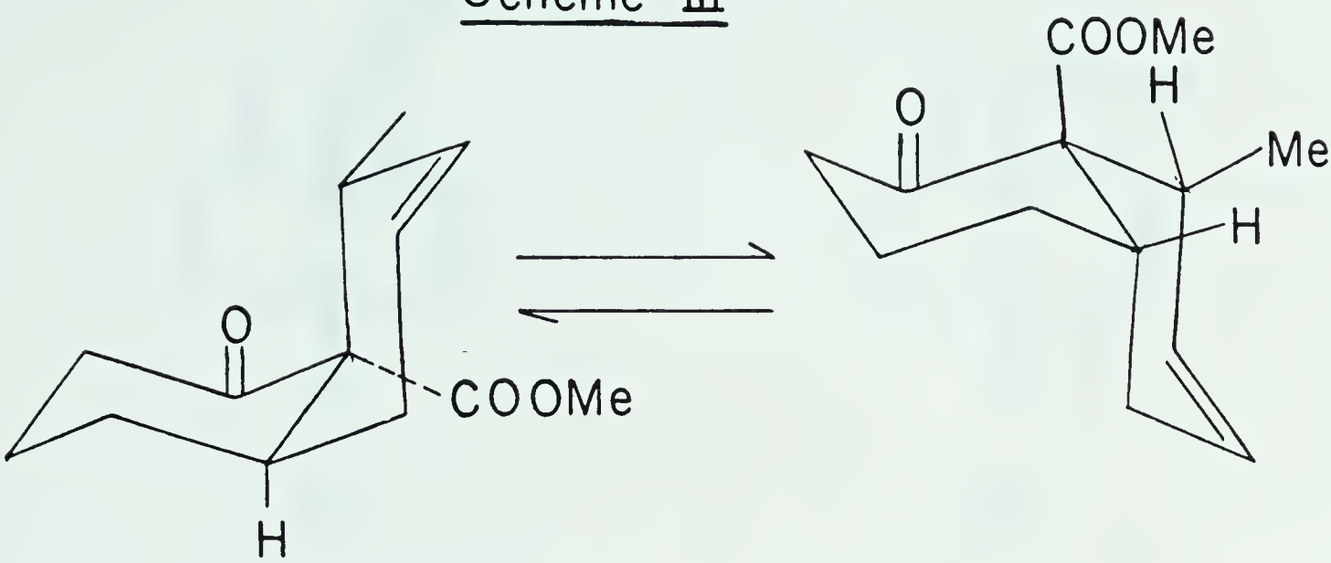
Scheme III



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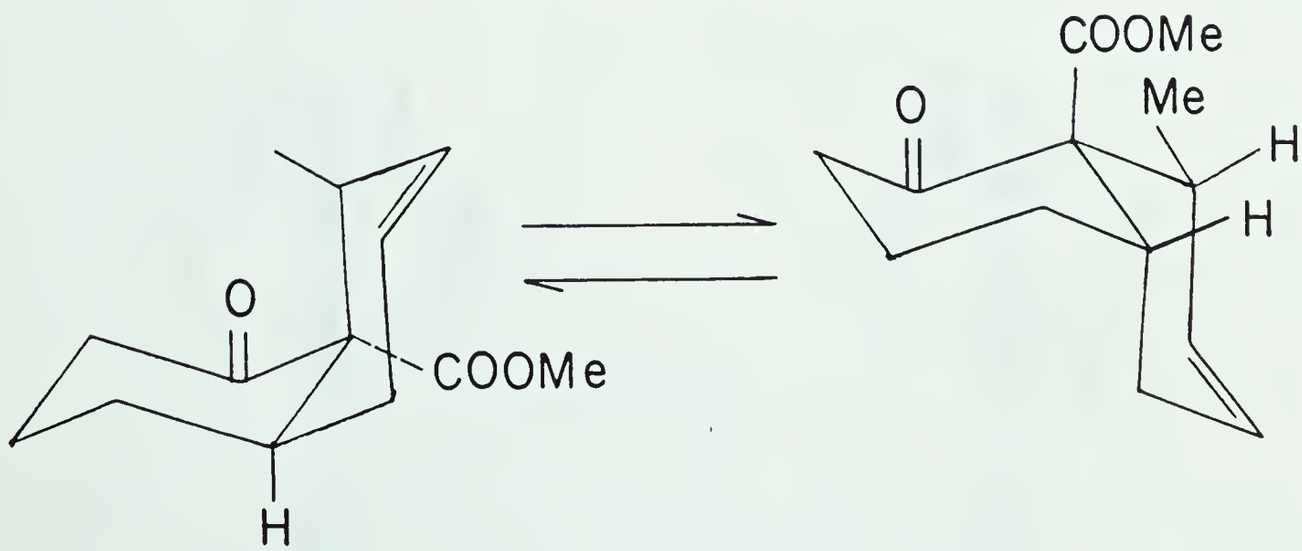

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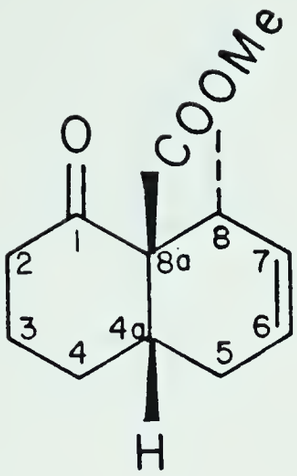

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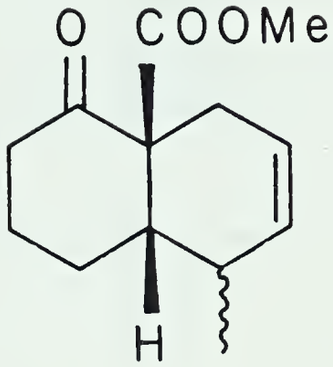

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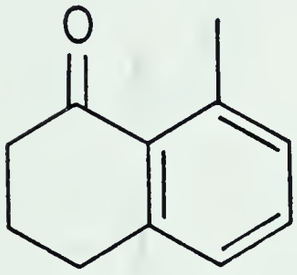

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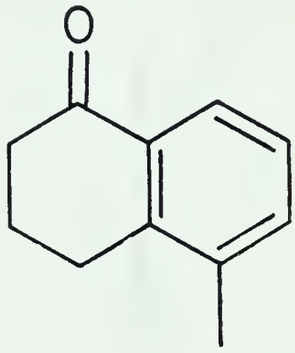

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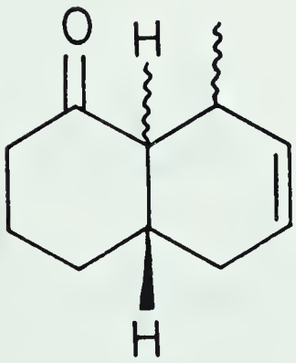

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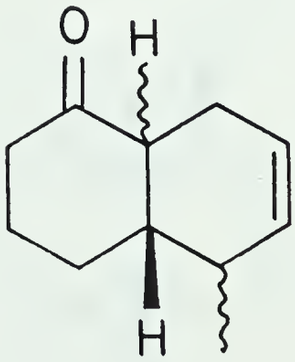

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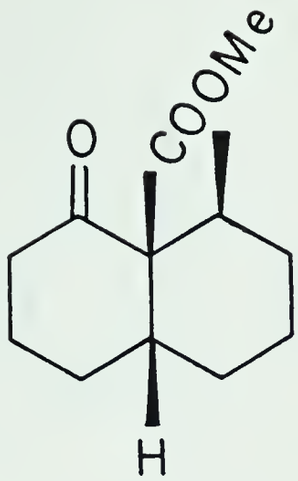

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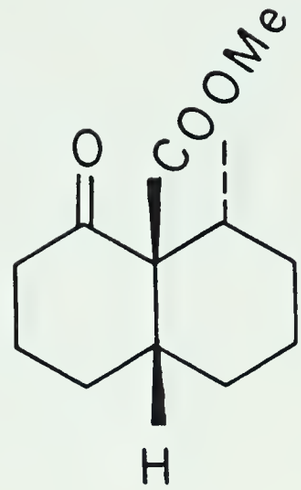

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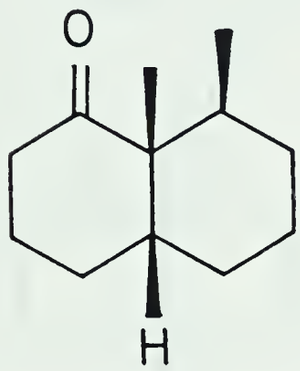

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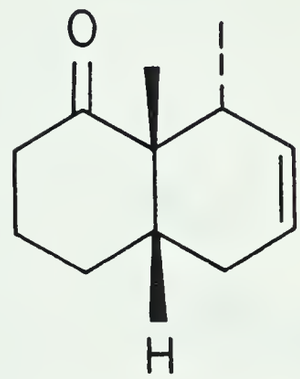

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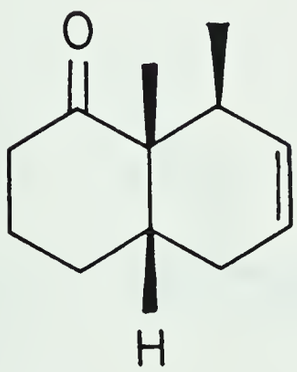

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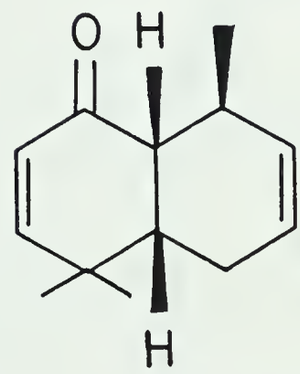

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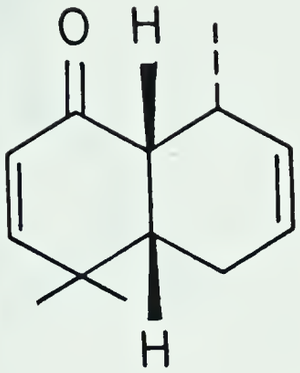

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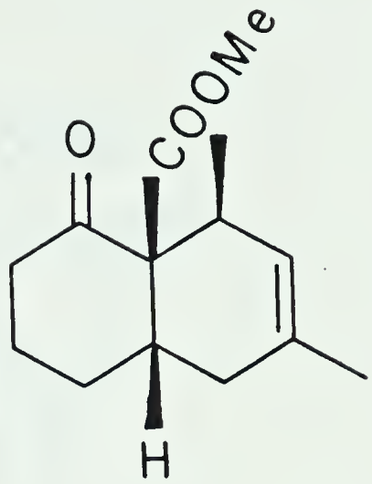

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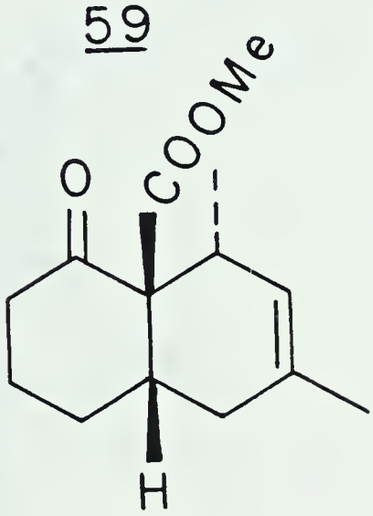

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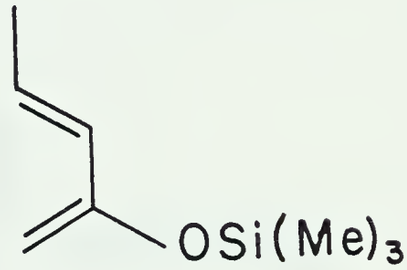

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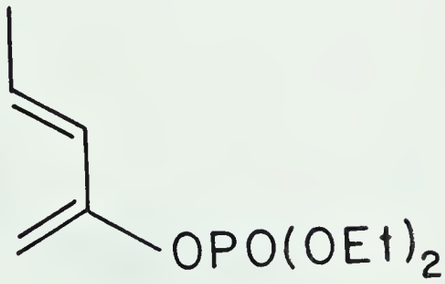

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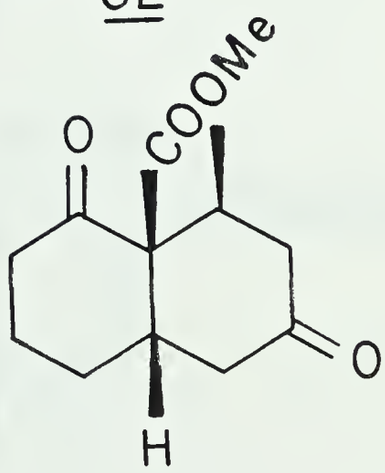

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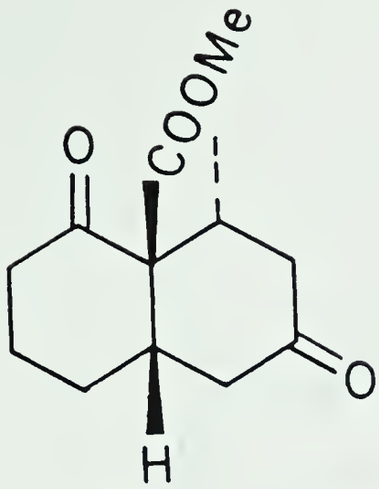

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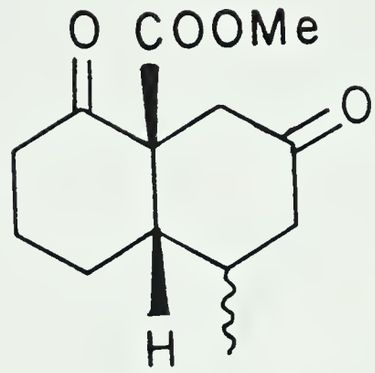

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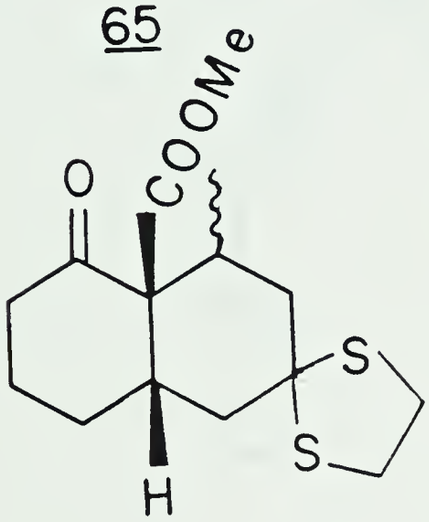

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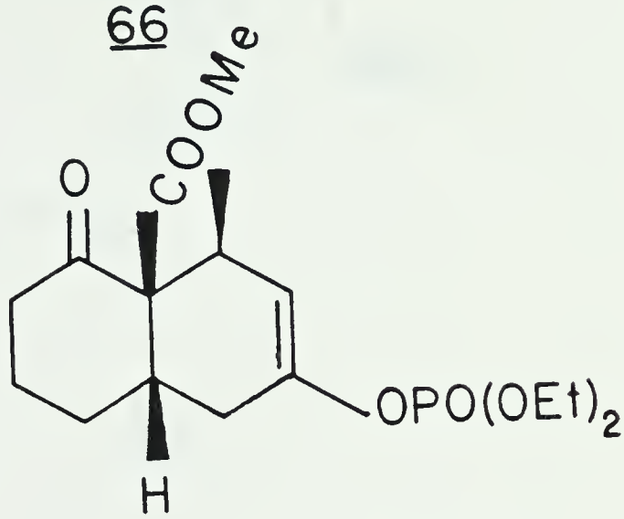

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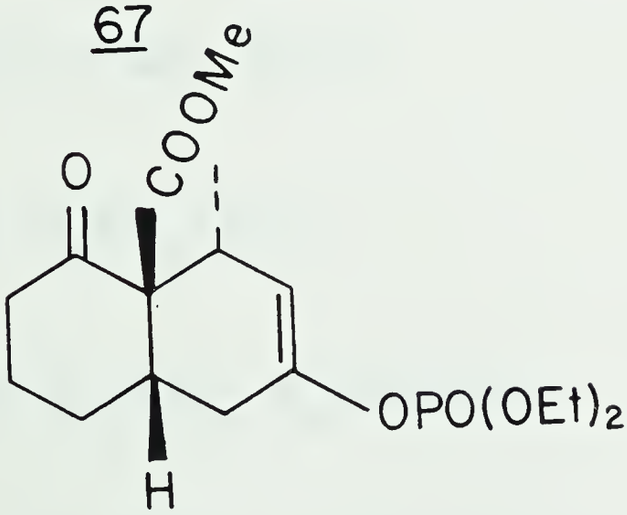

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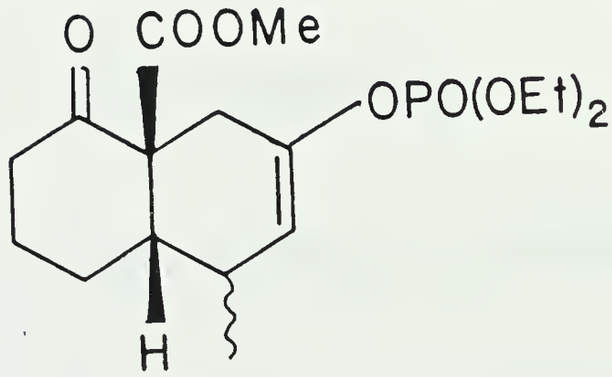

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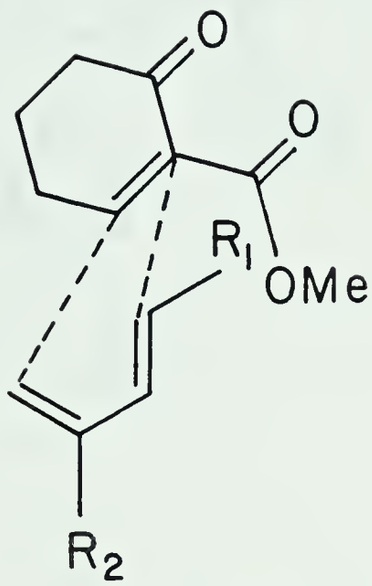

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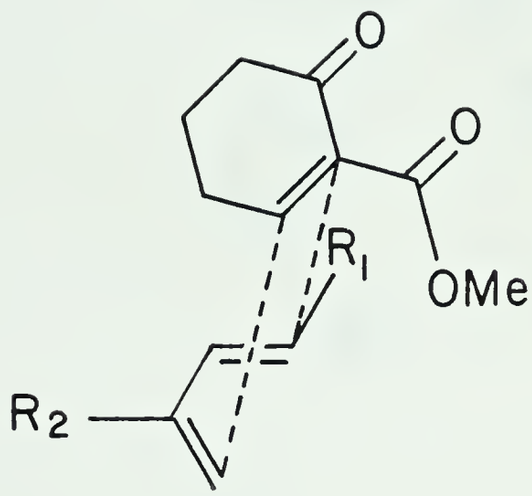

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71a : $R_1 = CH_3$, $R_2 = H$

71b : $R_1 = R_2 = CH_3$

71c : $R_1 = CH_3$, $R_2 = OSi(Me)_3$

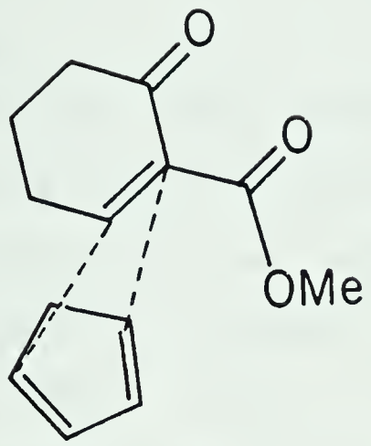
71d : $R_1 = CH_3$, $R_2 = OPO(OEt)_2$

72a : $R_1 = CH_3$, $R_2 = H$

72b : $R_1 = R_2 = CH_3$

72c : $R_1 = CH_3$, $R_2 = OSi(Me)_3$

72d : $R_1 = CH_3$, $R_2 = OPO(OEt)_2$



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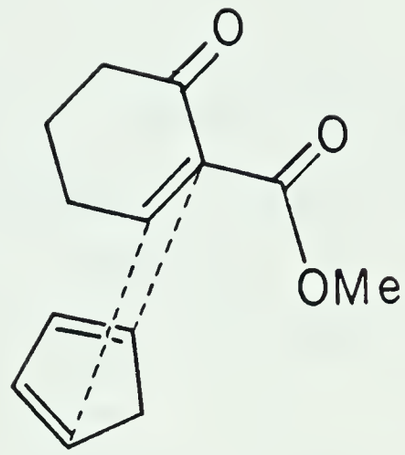

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Experimental

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analysis were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer and, except where otherwise stated, were obtained on solutions in carbon tetrachloride. Proton nuclear magnetic resonance (^{1}Hmr) spectra were recorded on a Varian HA-100, HA-100/Digilab or Bruker WH-200 and WH-400 spectrometer and, except where otherwise stated, were obtained on solutions in deuterochloroform with tetramethyl silane as internal reference. Carbon-13 nuclear magnetic resonance (^{13}Cmr) spectra were recorded on a Bruker HFX-90/Nicolet 1085 system or Bruker WH-200 and WH-400 and were obtained on solutions in deuterochloroform using tetramethyl silane as internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometers. Unless otherwise stated, anhydrous magnesium sulfate was used for drying organic solutions. Crystalline samples were recrystallized and liquid samples were subjected to Kuhrgelrohr distillation before submitting for elemental analysis.

Materials

Benzene, ether, tetrahydrofuran and 1,2-dimethoxyethane were freshly distilled over lithium aluminum hydride. *n*-Hexane was purified by simple distillation for use in chromatographic purifications. Anhydrous stannic chloride was purchased from A.G. Fluka and used without further purification. Nitrogen or argon was passed through a purification train of Fieser's solution,[60] saturated aqueous lead acetate, concentrated sulfuric acid and potassium hydroxide pellets. 2-Trimethylsilyloxy-1,3-butadiene was prepared according to the procedure of Conia.[53,61] Flash chromatography developed by Still[62] was used routinely for purification and separation of product mixtures.

2-Carbomethoxycyclohexanone (**31**)

Sodium hydride (60% oil dispersion; 10.9 g, 0.28 mmol) and dimethyl carbonate (82.5 g, 0.92 mmol) were added to 1,2-dimethoxyethane (200 mL) and the resulting mixture heated to reflux. A solution of cyclohexanone (17.9 g, 0.18 mmol) in 1,2-dimethoxyethane (100 mL) was added dropwise over a period of 1 h. The resulting mixture was refluxed for 22 h and cooled to 0°C. Ice-cold 10% aqueous acetic acid was added slowly with stirring. The resulting solution

was extracted with ether. The organic extracts were further washed with water, dried, filtered and concentrated. The yellow oil was subjected to bulb-to-bulb distillation, collecting the distillate at 70°C/2.0 torr as a colorless oil (21.4 g; 75% yield). The oil was analysed to be **31** by spectroscopic analysis: ^{1}Hmr δ12.52 (s, ~0.8H, enolic proton), 3.72, 3.70 (each s, total 3H, $-COOCH_3$) and 2.40 to 1.50 (complex m, 8H, 4 x $-CH_2-$); ir 1750, 1720, 1660 and 1620 cm^{-1} (keto-enol mixture of β-keto ester); ms M^+ 156.0780 (Calcd. for $C_{18}H_{12}O_3$: 156.0787).

2-Carbomethoxy-2-cyclohexen-1-one (**28**)

Benzeneselenenyl chloride (6.99 g, 36.5 mmol) and pyridine (2.89 g, 36.5 mmol) were dissolved in methylene chloride (200 mL) at 0°C. After stirring for 5.0 min, a solution of 2-carbomethoxycyclohexanone (4.74 g, 30.4 mmol) in methylene chloride (30 mL) was added. After another 30 min, the reaction mixture was washed with two portions (each 100 mL) of ice-cold 1.0 N aqueous hydrochloric acid. The organic layer was then transferred to the reaction flask and cooled to 0°C. A 30% aqueous hydrogen peroxide solution (6.0 mL) was added. After stirring for 10 min, additional 30% aqueous hydrogen peroxide (6.0 mL) was added. After 20 min, water was added and the layers separated. The organic

layer was washed with saturated aqueous sodium bicarbonate, dried, filtered and concentrated. The resulting product was obtained as a light yellow oil (4.6 g; ~100% yield) which was analysed to be **28** by spectroscopic analysis: ^{1}Hmr δ7.84 (t, 1H, J = 4.0 Hz, C=CH-) and 3.86 (s, 3H, $-COOCH_3$); ir ($CHCl_3$) 1750 (ester C=O) and 1715 cm^{-1} (ketone C=O); ms M^+ 154.0627 (Calcd. for $C_8H_{10}O_3$: 154.0630).

General conditions for the Diels-Alder reaction of enone-ester **28** using different Lewis acids.

Enone-ester **28** (1.0 eq) and the diene (2,3-dimethyl-butadiene or isoprene; 10 eq) were dissolved in ether at 0°C. The Lewis acid (boron trifluoride etherate, ferric chloride or stannic chloride; 0.5 eq) was added. After stirring under an atmosphere of argon 1-2 h as indicated in Table 1, saturated aqueous sodium bicarbonate was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Purification of the residue by flash chromatography gave either **33** or **34**. The results are summarized in Table 1.

8aβ-Carbomethoxy-6,7-dimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**33**).*

To a solution of enone-ester **28** (531 mg, 3.45 mmol) and 2,3-dimethyl-1,3-butadiene (2.8 g, 34.4 mmol) in ether (10 mL) at 0°C and under an atmosphere of argon was added anhydrous stannic chloride (0.44 g, 1.70 mmol). After stirring for 1.5 h at 0°C, saturated aqueous sodium bicarbonate (50 mL) was added and the resulting mixture was filtered through celite. The filtrate was extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Purification of the residue by flash chromatography on silica gel, eluting with a solution of 8% ethyl acetate in petroleum ether gave the keto-ester **33** (499 mg; 61% yield) which crystallized on standing. Recrystallization from a solution of ether in n-hexane gave white crystals of pure keto-ester **33**, m.p. 69-70°C: ^{1}Hmr δ3.72 (s, 3H, $-COOCH_3$) and 1.64 (br.s, 6H, 2 x $-CH_3$); ^{13}Cmr δ208.0, 172.8, 123.1, 121.7, 61.7, 52.2, 38.1, 37.6, 33.9, 33.5, 16.9, 23.9, 18.9 and 18.5; ir 1743 (ester C=O) and 1717 cm^{-1} (ketone C=O); ms M^+ 236.1414 (Calcd. for $C_{14}H_{20}O_3$: 236.1413).

*The stereochemical designations used in this and all other chemical names used in this section denote relative stereochemistry. All compounds used and obtained were racemic.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.02, H, 8.58.

8aβ-Carbomethoxy-6-methyl-3,4,5aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**34**).

Enone-ester **28** (1.37 g, 8.90 mmol) was dissolved in ether (20 mL) and cooled to 0°C. Isoprene (6.10 g, 89.7 mmol) and anhydrous stannic chloride (1.16 g, 4.45 mmol) were sequentially added. After stirring under an atmosphere of argon at 0°C for 6 h, water was added and the resulting mixture extracted with ether. The organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 7% ethyl acetate in petroleum ether gave the keto-ester **34** (1.20 g, 61% yield): ^{1}Hmr δ5.32 (m, 1H, -C=CH-), 3.73 (s, 3H, $-COOCH_3$) and 1.63 (s, 3H, $-CH_3$); ^{13}Cmr δ208.3, 172.8, 131.5, 116.8, 60.6, 52.3, 38.1, 37.5, 32.2, 27.8, 27.0, 24.1 and 23.6; ir (film) 1743 (ester C=O) and 1715 cm^{-1} (ketone C=O); ms M^+ 222.1256 (Calcd. for $C_{13}H_{18}O_3$: 222.1256).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 70.20; H, 8.20.

6-Methyl-3,4,4aβ 5,8,8aβ-hexahydro-1(2H)-naphthalenone (**40**).

Finely divided anhydrous lithium iodide (750 mg, 5.60 mmol) was suspended in 2,4,6-collidine (5.0 mL) with vigorous stirring. Water (0.20 μl, 11.2 mmol) was added and the suspension rapidly dissolved. Keto-ester **34** (580 mg, 2.60 mmol) was dissolved in this solution under an atmosphere of argon. The mixture was heated at reflux for 16 h. After cooling the mixture to room temperature, it was poured into ice-cold aqueous 1.0 N hydrochloric acid and extracted with ether. The extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave a mixture of epimeric ketones **40** (170 mg; 40% yield): ^{1}Hmr (CCL_4) δ5.37 (m, 1H, -C=CH-) and 1.60 (br.s, 3H, $-CH_3$); ir (film) 1714 cm^{-1} (ketone); ms M^+ 164.1197 (Calcd. for $C_{11}H_{16}O$: 164.1197).

6-Methyl-3,4-dihydro-1(2H)-naphthalenone (**36**).

The mixture of epimeric ketones **40** (140 mg, 0.85 mmol) was dissolved in carbon tetrachloride (10 mL). Benzoyl peroxide (5 mg, 0.02 mmol) and N-bromosuccinimide (310 mg, 1.74 mmol) were added. The reaction mixture was heated at reflux for 16 h under an atmosphere of argon. Filtration

and concentration gave an oily residue which was subjected to flash chromatography on silica gel. Elution with 5% ethyl acetate in petroleum ether afforded aryl-ketone **36** (87 mg; 64% yield): ^{1}Hmr δ7.92 (d, 1H, J = 8.0 Hz, C-8 H), 7.10 (d, 1H, J = 8.0 Hz, C-7 H), 7.04 (s, 2H, C-5 H), 2.90 (t, 2H, J = 6.0 Hz, $-CH_2-CO-$), 2.61 (dd, 2H, J = 8.0 Hz, J' = 6.0 Hz, $=C-CH_2-$), 2.37 (s, 3H, $-CH_3$) and 2.11 (m, 2H, $-CH_2-$); ^{13}Cmr δ197.9 (C-1), 144.5 (C-4a), 144.1 (C-8a), 130.6 (C-6), 129.2, 127.6, 127.4 (C-5, C-7 and C-8), 39.2 (C-2), 29.9 (C-4), 23.5 (C-3) and 21.6 ($-CH_2$); ir (film) 1682 (ketone) and 1608 cm^{-1} (aromatic C=C); ms M^+ 160.0879 (Calcd. for $C_{11}H_{12}O$: 160.0887).

<u>8aβ-Carbomethoxy-2,3,4,4aβ,5,7,8,8a-Octahydro-1,6-naphthalenedione (**41**).</u>

At 0°C, to a solution of enone-ester **28** (568 mg, 3.69 mmol) and 2-trimethylsilyloxy-1,3-butadiene (2.8 g, 18.5 mmol) in ether (20 mL) and under an atmosphere of argon, was added anhydrous stannic chloride (479 mg, 1.84 mmol). After stirring for 4 h, water was added and the resulting mixture extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. The crude residue was subjected to flash chromatography on silica gel. Elution with a solution of 20% ethyl acetate in petroleum ether gave the diketone **41** (212 mg; 27% yield).

Recrystallization from a solution of ether in petroleum ether gave white crystals of pure **41**: m.p. 87-88°C; ^{1}Hmr δ3.82 (s, 3H, $-COOCH_3$), 3.11 (ddd, 1H, J = 14 Hz, J' = 7.0 Hz, J" = 3.5 Hz, C-4a H) and 2.29 (d, 2H, J = 7.0 Hz, C-5 H); ^{13}Cmr δ209, 206, 171, 60, 52, 43, 42, 38, 37, 29, 27 and 23; ir 1736 (ester C=O) and 1714 cm^{-1} (ketone C=O); ms M^+ 224.1049 (Calcd. for $C_{12}H_{16}O_4$: 224.1049).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.18.

8aβ-Carbomethoxy-5-,8α-methano-3,4,4aβ 5,8,8a-hexahydro-1(2H)-naphthalenone (**44**).

To a solution of enone-ester **28** (428 mg, 2.78 mmol) and 1,3-cyclopentadiene* (2.0 g, 30.3 mmol) in ether (20 mL) at -25°C and under an atmosphere of argon, was added anhydrous stannic chloride (360 mg, 1.38 mmol). After stirring for 3 h, water was added and the resulting mixture extracted with chloroform. The organic extracts were further washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-10% ether in petroleum ether gave an impure fraction

*1,3-Cyclpentadiene was prepared by thermal cracking of dicyclopentadiene and was used immediately after the distillation.

containing the adduct **44**. Another purification with column chromatography on neutral alumina, eluting with a solution of 20% ethyl acetate in petroleum ether gave pure adduct **44** (174 mg; 29% yield). Recrystallization from n-hexane gave white crystals of pure **44**: m.p. 91-93°C; ^{1}Hmr δ6.31 (dd, 1H, J = 5.5 Hz, J' = 3.0 Hz, C-6 H), 6.00 (dd, 1H, J = 5.5 Hz, C-7 H), 3.67 (s, 3H, $-COOCH_3$), 3.63 (sharp m, 1H, C-8 H), 2.60 (sharp m, 1H, C-5 H), 2.52 (ddd, J = 12 Hz, J' = 7.0 Hz, J" = 2.0 Hz, C-4a H), 1.42 (ddd, J = 9.0 Hz, J' = 2.0 Hz, J" = 1.0 Hz, bridge -CHH-); ^{13}Cmr δ208.8, 171.1, 139.5, 138.8, 81.7, 52.5, 48.4, 47.5, 46.8, 45.9, 38.4, 29.4 and 20.9; ir 1730 (ester C=O) and 1709 cm^{-1} (ketone C=O); ms M^+ 220.1098 (Calcd. for $C_{13}H_{16}O_3$: 220.1100).

8aβ-Carbomethoxy-8β-methyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**46**) and 8aβ-carbomethoxy-8α-methyl-3,4,4aβ5,8,8a-hexahydro-1(2H)-naphthalenone (**47**).

a) From Diels-Alder reaction at 0°C.

To a solution of enone-ester **28** (453, 2.94 mmol) and trans-piperylene (2.0 g, 29.4 mmol) in ether (20 mL) at 0°C and under an atmosphere of argon, was added anhydrous stannic chloride (374 mg, 1.44 mmol). After stirring for 5 h, water was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with

water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1-5% ether in petroleum ether gave an impure mixture of adducts **46** and **47.** Further purification by column chromatography on neutral alumina (Woelm III), eluting with 10% ethyl acetate in petroleum ether gave a mixture of pure adducts **46** and **47** (182 mg; 28% yield). The mixture showed the following spectral data: ir (film) 1743 (ester C=O) and 1717 cm^{-1} (ketone C=O); ms M^+ 222.1256 (Calcd. for $C_{13}H_{18}O_3$: 222.1256). The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 5:4. One set, assignable to the major adduct **46**, showed signals at δ5.32 (m, 2H, -CH=CH-), 3.72 (s, 3H, $-COOCH_3$), 2.92 (m, 1H, $-C\underline{H}-CH_3$) and 0.83 (d, 3H, J = 7.0Hz, $-CH-C\underline{H_3}$); the other set, assignable to the minor adduct **47** showed signals at δ5.63 (m, 2H, -CH=CH-), 3.78 (s, 3H, $-COOCH_3$), 2.49 (m, 1H, $-C\underline{H}-CH_3$) and 1.17 (d, 3H, $-CH-C\underline{H_3}$).

b) <u>From Diels-Alder reaction at -30°C</u>.

To a solution of enone-ester **28** (331 mg, 2.15 mmol) and <u>trans</u>-piperylene (1.5 g, 22.0 mmol) in ether (10 mL) at -30°C and under an atmosphere of nitrogen, was added anhydrous stannic chloride (2.86 mg, 1.09 mmol). After stirring for 6 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture

extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on neutral alumina eluting with 10% ethyl acetate in petroleum ether gave in impure mixture of adducts **46** and **47.** Another chromatographic purification on neutral alumina (Woelm III), eluting with 10% ethyl acetate in petroleum ether gave a pure 5:3 mixture (by ^{1}Hmr itegration) of adducts **46** and **47** (164 mg; 34% yield).

c) <u>From Diels-Alder reaction at -78°C</u>.

To a solution of enone-ester **28** (408 mg, 2.65 mmol) and <u>trans</u>-piperylene (1.8 g, 26.5 mmol) in ether (15 mL) at -78°C and under an atmosphere of nitrogen, was added anhydrous stannic chloride (352 mg, 1.35 mmol). After stirring for 6 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. Column chromatography of the residue on neutral alumina (Woelm III) gave an impure mixture of adducts **46** and **47.** Another purification on neutral alumina (Woelm III), eluting with 10% ethyl acetate in petroleum ether gave a pure 5:3 mixture (by ^{1}Hmr integration) of adducts **46** and **47** (200 mg; 34% yield).

Mixture of ketones **51**.

Finely divided anhydrous lithium iodide (101 mg, 0.74 mmol) was suspended in 2,4,6-collidine (5 mL) with vigorous stirring. Water (27 mg, 1.51 mmol) was added and the suspension dissolved on vigorous stirring. A 5:4 mixture of keto-esters **46** and **47** (84 mg, 0.38 mmol) was added to the lithium iodide dihydrate solution. The mixture was heated to reflux for 1.5 h undr an atmosphere of nitrogen. The reaction mixture was cooled to room temperature and poured into ice-cold aqueous 1.0 N hydrochloric acid and extracted with methylene chloride. The extracts were further washed with aqueous 1.0 N hydroxhloric acid, water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with a solution of 5% ether in petroleum ether gave a mixture of three ketones **51** (51 mg; 82% yield). The mixture of ketones **51** showed the following spectral data: ^{1}Hmr δ1.00, 0.99, 0.98 (each d, total 3H each J = 7.0 Hz, CH-$\underline{CH_3}$) and 5.56 (complex m, total 2H, -CH=CH-); ir (film) 1712 cm^{-1} (ketone); ms M^+ 164.1198 (Calcd. for $C_{11}H_{16}O$: 164.1201).

8-Methyl-3,4-dihydro-1(2H)-naphthalenone (**49**).

A mixture of ketones **51** (51 mg, 0.31 mmol) was dissolved in carbon tetrachloride (10 mL). Benzoyl peroxide (5 mg, 0.02 mmol) and N-bromosuccinimide (110 mg, 0.62 mmol) were added. The reaction mixture was heated to reflux for 10 h under an atmosphere of nitrogen and cooled to room temperature. Filtration and concentration gave an oily residue which was purified by flash chromatography on silica gel. Elution with 10% ether in petroleum ether gave aryl-ketone **49** (29 mg; 58% yield): ^{1}Hmr δ7.30 (m, 2H, 2 x aromatic H), 7.10 (d, 1H, J = 7.0 Hz, aromatic H), 2.95 (t, 2H, J = 6.0 Hz, $-CH_2-C=O$), 2.65 (t, 2H, J = 7.0 Hz, $-CH_2-C=$), 2.63 (s, 3H, $-CH_3$) and 2.50 (m, 2H, $-CH_2\underline{CH_2}-CH_2-$); ir (film) 1690 (C=O); ms M^+ 160.0871 (Calcd. for $C_{11}H_{12}O$: 160.0888).

8aβ-Carbomethoxy-8β-methyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (**53**) and 8aβ-carbomethoxy-8α-methyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (**54**).

a) From Diels-Alder adducts **46** and **47**.

A 5:4 mixture of Diels-Alder adducts **46** and **47** (540 mg, 2.43 mmol) and Raney-nickel (*ca.* 5.0 g, grade W-2) were placed in ethanol (15 mL). After stirring for 7 h, the

reaction mixture was filtered and the organic filtrate concentrated. Column chromatography of the residue on silica gel, eluting with a solution of 1% ethyl acetate in petroleum ether gave pure keto-ester **54** (198 mg; 36% yield) as a colorless oil: ^{1}Hmr δ3.79 (s, 3H, $-COOCH_3$) and 1.18 (d, 3H, J = 7.0 Hz, $CH-C\underline{H}_3$); ir (neat) 1739 (ester C=O) and 1712 cm^{-1} (ketone C=O); ms M^+ 224.1410 (Calcd. for $C_{13}H_{20}O_3$: 224.1407). Continued elution gave the isomeric keto-ester **53** (263 mg; 48% yield) which crystallized on standing: m.p. 37-39°C; ^{1}Hmr δ3.72 (s, 3H, $-COOCH_3$) and 0.86 (d, 3H, J = 7.0 Hz, $CH-C\underline{H}_3$); ir 1740 (ester) and 1714 cm^{-1} (ketone); ms M^+ 224.1411 (Calcd. for $C_{13}H_{20}O_3$: 224.1407).

<u>Anal</u>. Calcd. for $C_{13}H_{20}O_3$: C, 69.91; H, 8.99. Found: C, 69.77; H, 9.01.

b) <u>From thioketals **67**</u>.

To a solution of a 3:1 mixture of thioketals **67** (31 mg, 0.09 mmol) in dry ethanol (5.0 mL) was added Raney-nickel (<u>ca</u>. 0.5 g, grade W-2) under an atmosphere of nitrogen. The mixture was heated to reflux for 5 h and cooled to room temperature. Filtration and concentration gave a light yellow oil which was purified by column chromatography on silical gel. Elution with 2% ether in petroleum ether gave the minor keto-ester **54** (3.0 mg; 14% yield). Continued elution gave the major keto-ester **53** (11 mg; 50% yield).

c) From the mixture of enol-phosphate **68** and **69**.

A 6:1 mixture of enol-phosphates **68** and **69** (528 mg, 1.41 mmol) and platinum oxide (52 mg) were added to ethyl acetate (20 mL). The reaction mixture was hydrogenated at one atmosphere of hydrogen pressure for 1 h. Filtration and concentration gave an oil which was purified by flash chromatography on silica gel. Elution with 10% ether in petroleum ether gave the keto-ester **54** (35 mg; 11% yield). Continued elution gave the isomeric keto-ester **53** (241 mg; 76% yield).

8aβ-Carbomethoxy-6,8β-dimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**60**) and 8aβ-Carbomethoxy-6-8α-dimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**61**).

a) From Diels-Alder reaction at 0°C.

To a solution of enone-ester **28** (505 mg, 3.28) in eher (10 mL) at 0°C and under an atmosphere of argon, were sequentially added trans-2-methyl-1,3-pentadiene (808 mg, 9.85 mmol) and anhydrous stannic chloride (427 mg, 1.64 mmol). After stirring for 3 h, water was added and the resulting mixture was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on

silica gel, eluting with 5-10% ethyl acetate in petroleum ether gave an impure mixture of adducts **60** and **61**. Another purification by flash chromatography, eluting with a solution of 6% ethyl acetate in petroleum ether gave a mixture of pure adducts **61** and **62** (2.55 mg; 34% yield). The mixture of adducts showed the following spectral data: ir (neat) 1740 (ester) and 1716 (ketone); ms M^+ 236.1413 (Calcd. for $C_{14}H_{20}O_3$: 236.1413). The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 2:1. One set assignable to the major keto-ester **60**: δ5.25 (m, 1H, -C=CH-), 3.63 (s, 3H, $-COOCH_3$), 2.83 (m, 1H, $-C\underline{H}-CH_3$) and 0.73 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H}_3$); the other set, assignable to the minor keto ester **61**: δ5.15 (m, 1H, -C=CH-), 3.70 (s, 3H, $-COOCH_3$), 2.40 (m, 2H, $-C\underline{H}-CH_3$), and 1.08 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H}_3$).

b) <u>From Diels-Alder reaction at -35°C</u>.

Enone-ester **28** (574 mg, 3.73 mmol) and <u>trans</u>-2-methyl-1,3-pentadiene (0.92 g, 11.2 mmol) were placed in ether (10 mL) and cooled to -35°C. Anhydrous stannic chloride (485 mg, 1.86 mmol) was added. After stirring under an atmosphere of argon for 3 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture was extracted with methylene chloride. The combined organic extracts was dried, filtered and concentrated.

Column chromatography of the residue on silica gel, eluting wih 5% ethyl acetate in petroleum ether gave an impure mixture of adducts **60** and **61.** Another chromatographic purification on nuetral alumina (Woelm III), eluting with 50% ether in petroleum ether gave a 6:1 mixture (by ^{1}Hmr integration) of adduct **60** and **62** (299 mg; 34% yield).

c) From Diels-Alder reaction at -78°C.

To a solution of enone-ester **28** (238 mg, 1.54 mmol) in ether (8 mL) at -78°C and under an atmosphere of argon, were sequentially added trans-2-methyl-1,3-pentadiene (380, 4.64 mmol) and anhydrous stannic chloride (201 mg, 0.77 mmol). After stirring for 6 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture was extracted with methylene chloride. The combined organic extracts was dried, filtered and concentrated. Column chromatography of the residue on neutral alumina (Woelm III), eluting with a solution of 20-50% ether in petroleum ether gave an impure mixture of adducts **60** and **61.** Another chromatographic purification on neutral alumina (Woelm III), eluting with 50% ether in petroleum ether gave a 13:1 mixture (by ^{1}Hmr integration) of adducts **60** and **61** (136 mg; 37% yield). Fractional recrystallization of the mixture from ether/petroleum ether gave white crystals of pure **60**: m.p. 110-111°C; ^{1}Hmr δ5.34 (m, 1H, -C=CH-), 3.74 (s, 3H,

$-COOCH_3$), 2.92 (m, 1H, $-C\underline{H}-CH_3$) and 0.83 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H}_3$).

trans-2-Trimethylsilyloxy-1,3-pentadiene (**62**)

At -78°C and under an atmosphere of argon, n-butyllithium (56.7 mL of 1.5 M in n-hexane, 85.0 mmol) was added to a solution containing diisopropylamine (8.59 g, 84.9 mmol) in tetrahydrofuran (40 mL). After stirring for 15 min, a solution of trans-3-penten-2-one (6.48 g, 77.0 mmol) in tetrahydrofuran (20 mL) was added dropwise over 10 min through a pressure equalizing dropping funnel. After another 20 min, chlorotrimethylsilane (16.8 g, 154 mmol) was rapidly added. The resulting solution was allowed to warm to room temperature. n-Pentane was added to the reaction mixture and the resulting solution was washed with ice-cold distilled water (400 mL). The organic layer was dried, filtered and concentrated. The residue was fractionally distilled, collecting the fraction from 56-62°C at 16 torr. The resulting colourless oil was analysed to be the required diene **62** (6.7 g, 54% yield): ^{1}Hmr δ5.88, 5.30 (both m, total 2H, -CH=CH-), 4.07 (br.s, 2H, $-C=CH_2$), 1.80 (m, 3H, $=CH-C\underline{H}_3$) and 0.18 (s, 9H, $-Si(CH_3)_3$); ir 2960, 1569, 1507, 1256 and 1048; ms M^+ 159.0968 (Calcd. for $C_8H_{16}OSi$: 156.0971).

Diethyl trans-1,3-pentadien-2-yl phosphate (**63**)

To a solution of diisopropylamine (4.1 g, 40.3 mmol) in tetrahydrofuran (50 mL) at -78°C and under an atmosphere of argon, was added methyllithium (36.3 mL of 1.1 M in n-hexane, 40.3 mmol). After stirring for 10 min, a solution of trans-3-penten-2-one (3.1 g, 36.7 mmol) in tetrahydrofuran (20 mL) was added dropwise over 10 min. After stirring for another 15 min, diethylchlorophosphate (13.8 g, 80.0 mmol) was added. The reaction mixture was allowed to warm up to room temperature. Ice-cold water was added and the resulting mixture extracted with n-pentane. The organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the resulting dark yellow oil, eluting with a solution of 50% ether in petroleum ether gave the required diene **63** (3.5 g, 44% yield); ^{1}Hmr δ6.32 to 5.70 (m, 2H, -C<u>H</u>=C<u>H</u>-), 4.82 (m, 1H, =CH<u>H</u>), 4.60 (m, 1H, =C<u>H</u>H), 4.17 (dq, 4H, J = J' = 7.0 Hz, 2 x $-CH_2-$), 1.80 (d, 3H, J = 5.5 Hz, =CH-C<u>H</u>$_3$) and 1.35 (t, 6H, J = 7.0 Hz each, 2x $-OCH_2C\underline{H}_3$); ir 1275 and 1270 cm^{-1} (both P=O); ms M^+ 220.0865 (Calcd. for $C_9H_{17}O_4P$: 220.0865).

8aβ-Carbomethoxy-8β-methyl-2,3,4,4,aβ,5,7,8,8a-octahydro-1,6-naphthalenedione (**64**) and 8aβ-carbomethoxy-8α-methyl-2,3,4,4aβ,5,7,8,8a-octahydro-1,6-naphthalenedione (**65**).

Enone-ester **28** (179 mg, 1.16 mmol) was dissolved in ether (5 mL) and cooled to -30°C. trans-2-Trimethylsilyloxy-1,3-pentadiene (**62**) (560 mg, 3.59 mmol) and anhydrous stannic chloride (151 mg, 0.58 mmol) were sequentially added. After stirring at -30°C and under an atmosphere of nitrogen for 4.5 h, the reaction mixture was warmed to room temperature and water was added. The resulting mixture was extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. The crude residue was purified by flash chromatography. Elution with 10% ethyl acetate in petroleum ether gave a 3.3:1 mixture (by ^{1}Hmr integration) of keto-esters **64** and **65** (86 mg; 45% yield). The mixture of keto-esters **64** and **65** has the following spectral data: ir 1740 (ester C=O) and 1714 cm^{-1} (ketone C=O); ms M^+ 238.1205 (Calcd. for $C_{13}H_{22}O_4$: 238.1205). The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 3.3:1. The major set, assignable to **64** showed signals at δ3.73 (s, 3H, $-COOCH_3$) and 0.90 (d, J = 7.0 Hz, $-CH-C\underline{H}_3$); the minor set, assigned to **65**, showed signals at δ3.82 (s, 3H, $-COOCH_3$) and 1.15 (d, 3H, $-CH-C\underline{H}_3$).

8aβ-Carbomethoxy-6-diethylphosphoryloxy-8β-dimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**68**) and 8aβ-Carbomethoxy-6-diethylphosphoryloxy-8βα-dimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (**69**).

At -30°C, anhydrous stannic chloride (294 mg, 1.13 mmol) was added to a solution of enone-ester **28** (348 mg, 2.26 mmol) and phosphate diene **63** (698 mg, 3.17 mmol) in ether (10 mL). After stirring under an atmosphere of nitrogen for 6 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture extracted with methylene chloride. The organic extrcts were combined, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 50% ethyl acetate in n-hexane gave the diene **63** (180 mg; 26% recovery). Continued elution gave the pure enol-phosphates **68** and **69** (555 mg; 66% yield) in a ratio of 6:1. The mixture showed the following spectral data: ir 1750 (ester C=O) and 1720 cm^{-1} (ketone C=O); ms M^+ 374.1495 (Calcd. for $C_{17}H_{27}O_7$: 374.1495). The ^{1}Hmr spectrum of the mixture of adducts showed two sets of signals in an integral ratio of 6:1. The major set, assignable to **68**, showed signals at δ5.47 (m, 1H, -C=CH-), 4.15 (m, 4H, 2x $-O\underline{CH_2}CH_3$), 3.75 (s, 3H, $-COOCH_3$), 1.37 (t, 6H, J = 7.0 Hz, 2x $-OCH_2C\underline{H_3}$) and 0.92 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H_3}$); the other set, assignable to **69**

showed signals at δ5.34 (m, 1H, C=CH-), 4.15 (m, 4H, 2x $-OC\underline{H}_2CH_3$), 3.80 (s, 3H, $-COOCH_3$), 1.37 (t, J = 7.0 Hz, 6H, 2x $-OCH_2C\underline{H}_3$) and 1.24 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H}_3$).

Mixture of thioketals **67**.

At 0°C, to a solution of a 3.3:1 mixture of **64** and **65** (171 mg, 0.72 mmol) in methylene chloride (5 mL), were sequentially added 1,2-ethanedithiol (339mg, 3.60 mmol) and boron trifluoride etherate (112 mg, 0.79 mmol). After stirring under an atmosphere of argon for 25 min, ice-cold 2.0 N aqueous sodium hydroxide solution was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ether in n-hexane gave a 3.3:1 mixture of thioketals **67** (137 mg; 74% yield, based on consumed starting material). The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of 3.3:1. It consisted of signals at δ3.80, 3.74 (each s, total 3H, $-COOCH_3$), 3.30 (complex m, 4H, $-SCH_2CH_2S-$), 1.10, 1.02 (each d, total 3H, each J = 7.5 Hz, $CH-C\underline{H}_3$). The following spectral data were also recorded for the mixture of thioketals **67**: ir (film) 1740 (ester C=O) and 1713 cm^{-1} (ketone C=O); ms M^+ 314.1008 (Calcd. for $C_{15}H_{22}O_3S_2$:

314.1010). Continued elution gave the mixture of diketones **64** and **65** (31 mg; 18% recovery).

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CHAPTER 2

Total Synthesis of Petasitolone

Introduction

The eremophilane family of sesquiterpenes is an interesting class of nonisoprenoid compounds possessing the carbon skeleton as depicted by **1**. Prominent in these naturally occuring compounds, is the presence of the vicinal methyl groups on C-4 and C-5 which usually have the cis relative stereochemistry. Often present in the carbon skeleton are a rich array of oxygen and double-bond functionalities. The isolation of three representatives of this class from the Australian shrub *Eremophilia mitchelli* was first reported in 1932 by Penfold, Simonsen, and Bradfield[1]. The gross skeletal structures of these three sesquiterpenoids which were designated as eremophilone (**2**), hydroxyeremophilone (**3**) and hydroxydihydroeremophilone (**4**), were later elucidated after extensive investigations by Simonsen and collaborators.[2] The assignment of relative stereochemistry[3,4] of these compounds was confirmed by an X-ray diffraction analysis of hydroxydihydroeremophilone (**4**).[5] Later on, the absolute stereochemistry was established to be as shown in structures **2**, **3** and **4** by Djerassi and co-workers by an unequivocal chemical correlation[6] with the known (+)-ketone **5**.[7,8]

Since then, a large number of eremophilanes have been reported.[2,9] These sesquiterpenoids, numbering more than two hundred compounds, can be classified into two major structural types. The first type consists of those structures having only a bicyclic carbon framework as depicted by **1**. The second, having a tricyclic structure, is classified as the furanoeremophilanes wherein a furan or butenolide ring is fused onto the bicyclic eremophilane system at C-7 and C-8; the three carbon substituent at C-7 provides the two carbon atoms for the furan ring as in furanoeremophilane (**6**), a naturally occuring substance isolated from the rhizomes of Petasites officinalis Moench.[10]

Among the simplest members of the first group to be isolated, are eremophilene (**7**)[11] and isoeremophilene (**8**)[12] which are two structurally related hydrocarbons differing only in the position of one of the double-bonds. Initially, eremophilene was assigned to structure **9**[13] but was later confirmed to be incorrect by Piers and Keziere[14] who synthesized compound **9** but found its non-identity to the natural eremophilene. After a re-examination of its ^{1}Hmr spectrum, eremophilene was later reformulated as having structure **7**.[11]

A large number of oxygenated derivatives have been isolated. Prominent among them are fukinone (**10**),[15]

nootkatone (**11**),[16,17] isonootkatone (**12**)[18] (also known as α-vetivone) and eremoliginol (**13**).[19] All these structures have yielded to a number of syntheses, especially fukinone (**10**) and nootkatone (**11**). Another oxygenated derivative which was recently isolated from Petasites japonicus Maxim was designated as petasitolone (**14**).[20] Its structure was conclusively established, based on spectral evidence and chemical correlation with fukinone (**10**).[20]

Prior to 1974, very few furanoeremophilanes were isolated. The systematic investigations of Bohlmann and co-workers[2] of some South African plants of the Euryops, Othonna and Senecio families, have revealed the presence of a large number of furanoeremophilanes. Among the first to be isolated were ligularone (**15**),[21] furanoligularone (**16**),[22] euryopsol (**17**)[23] and euryopsonol (**18**).[24] Another type of furanoeremophilane containing a butenolide instead of a furan ring has also been isolated. Examples include eremophilenolide (**19**)[25] and ligularenolide (**20**).[26] The latter compound was isolated from the roots of Ligularia sibisica, a chinese herbal drug known as "San-Shion".

It was suggested by Robinson[27] that the eremophilanes are biogenetically derived from the eudesmanes class of sesquiterpenes. The eudesmanoid biosynthetic intermediate **21** was proposed to have undergone a 1,2-methyl migration which would give the cation **22**, a plausible intermediate in

the biosynthesis of the eremophilanoid sesquiterpenes (Scheme I). Results of biosynthetic studies[28] on capsidiol (**23**), a 4-epi-eremophilane indicated the likely occurence of such a methyl migration.

A successful attempt to mimic a direct C-10 to C-5 methyl migration in vitro has been reported.[29] Treatment of the epoxide **24** with formic acid gave the alcohol **25**, resulting from acid catalysed oxirane opening and a concomitant 1,2-methyl migration. Compound **25** was subsequently converted into tetrahydroligularenolide (**26**),[29] a chemical degradation product from ligularenolide (**20**).

The eremophilane family of sesquiterpenes has attracted a great deal of synthetic efforts during the past years.[30,31] A large number of these sesquiterpenes having diverse functionalities have yielded to total synthesis which employed a rich variety of synthetic methodologies. The synthetic problems associated with this class of compounds are two-fold. Firstly, the problem of stereoselective formation of the cis-stereochemistry for the vicinal methyl groups on C-4 and C-5. Related to the problem of control of relative stereochemistry, is the ring-junction stereochemistry which is usually cis, and the stereochemistry of the three-carbon side chain which exists either cis or trans to the angular methyl group. Secondly, an efficient method for the synthesis of a suitable decalin

derivative which has an appropriate level of functionalization has to be achieved.

Earlier synthetic efforts centred on the use of the Robinson annulation for the construction of the bicyclic framework. Several groups have studied this annulation process with a view of controlling the cis-stereochemistry of the vicinal methyls. For example, Marshall and co-workers[32] studied the annulation of the keto-ester **27** with trans-3-penten-2-one under a variety of reaction conditions and found a 3:1 ratio of enones **28** and **29** could be obtained in 65% yield; the major isomer **28** being required for eremophilane synthesis. They have successfully applied this finding to the total synthesis of (±)-nootkatone (**11**)[34] and isonootkatone (**12**).[33]

The results observed by Marshall and co-workers were interesting in view of other related works with 2-methyl-cyclohexane-1,3-dione (**30**). It gave the cis-isomer **31** as a minor product when the annulation was accomplished with potassium hydroxide and pyrrolidine[35] or on the pyrrolidine enamine of **30** in benzene.[36] The best result was obtained using the pyrrolidine enamine of **30** in dimethylformamide as the solvent.[36] It furnished a 1:1 mixture of the cis-enone **31** and trans-enone **32** in 27% yield. Although the stereoselectivity was moderate and the yield was low in the latter reaction, it formed the basis of the synthesis of

valencene (**33**), valerianol (**34**), eremophilene (**7**) and eremoliginol (**13**) by Coates and co-workers.[37]

Improved stereoselectivity was observed in the Robinson annulation of ketones **35** and **36** with trans-3-penten-2-one using sodium hydride in ether[38] and sodium amide in liquid ammonia[39] respectively. In the former reaction, the sole adduct **37**, obtained in 56% yield, was converted into (±)-nootkatone (**11**) and valencene (**33**) by Pinder and co-workers.[38] Adduct **38**, obtained in 50% yield in the latter reaction which was originally studied by Van der Gens[39] for eremophilane synthesis, was utilized by McMurry and co-workers[40] in a total synthesis of racemic eremophilone (**2**).

A different approach for the control of the stereochemistry of the cis vicinal methyls has been developed by Piers in his synthesis of fukinone (**10**). Previous works by Piers[41] and Ourisson[42] had shown that 2,3-dimethylcyclohexanone (**39**) could be used in a Robinson annulation with methyl vinyl ketone. However, it was found that a 15% yield of adducts was obtained and a 3:2 ratio of stereoisomers **40** and **41** was formed. It was further noted by Piers that alkylation of 2,3-dimethyl-6-n-butylthio-methylenecyclohexanone (**42**) with methallyl chloride produced a mixture of ketones **43** and **44**. The ratio of products was 4:1 in favor of the cis-ketone **43**. This finding led Piers

and co-workers to develop a total synthesis of fukinone (**10**).[43]

In the synthesis, ketone **42** was alkylated with ethyl 3-bromopropionate to give a mixture of keto-esters **45** which was converted in two steps into a 9:1 mixture of enol-lactones **46** and **47**. The major isomer **46** which was separated by fractional recrystallization was transformed into fukinone (**10**), as well as (±)-eremophilenolide (**19**) and (±)-tetrahydroligularenolide (**26**).[45]

Marshall and Cohen[46] have also developed a synthesis of (±)-fukinone (**10**) using a different approach for generating the cis stereochemistry for the vicinal methyl groups. Their approach involved the conjugate addition of lithium dimethylcuprate to the enone **49**, affording stereoselectively the required cis-ketone **50**. The stereoselectivity of the 1,4-addition was the result of the folded nature of the cis-octalone system. The enone **49** was prepared from o-anisaldehyde (**48**) by an eleven step sequence. Further transformation of ketone **50** gave (±)-fukinone (**10**) in eight steps.

Over the years, a number of syntheses of (±)-nootkatone (**11**) have been developed. Besides the syntheses already discussed, several groups have succeeded in synthesizing nootkatone (**11**) employing different approaches in controlling the stereochemistry of the vicinal methyl groups.

One of these syntheses is the imaginative and novel approach which was developed by Dastur[47] in 1973. The synthesis relied on the successful outcome of two key steps. The first step involved the Diels-Alder reaction of the diene **52** (which was generated *in situ* from the methyl ether **51**) with methyl acrylate in refluxing dichloromaleic anhydride to give adducts **53**. Although products arising both from *exo* and *endo* transition states were formed, addition of dienophile occurred only from the face that is *anti* to the secondary methyl group of the diene. Thus, although a mixture of epimers at the carbomethoxy position was obtained, the secondary methyl group was completely *syn* to the double-bond of the Diels-Alder adduct **53**. This outcome was important as it led to the *cis* disposition for the vicinal methyl groups after subsequent transformations. Adduct **53** was subjected to allylic oxidation with selenium dioxide to give the aldehyde **54**. Wittig reaction on the aldehyde group, followed by methyllithium addition gave the alcohol **55**.

The second key step to generate the bicyclic framework was achieved by treating alcohol **55** with formic acid. Under the solvolysis condition, the formate **56** was obtained. The transformation **55** → **56** can be rationalized as shown in Scheme II. The enone-formate **56** was converted into a 3:1 mixture of (±)-nootkatone (**11**) and (±)-isonootkatone (**12**) by saponification and dehydration.

Hiyama and co-workers[48] have developed a novel approach to (±)-nootkatone (**11**). In this approach, the control of the cis stereochemistry for the vicinal methyls was achieved by the cyclization of diol **59** in the presence of sulfuric acid in methanol. It furnished the indenone derivatives **60** which was a 3:2 mixture of stereoisomers at the carbomethoxy position. The stereoselectivity of the ring closure to give the cis stereochemistry in the product has been rationalized as the result of a conrotatory closure of the protonated dienone **61b** as depicted in Scheme III. Conversion of the 3:2 mixture of indenones **60** to give a single acetyl derivative **63** was achieved by a series of reactions which involved an epimerization at the center bearing the acetyl group to the required stereochemistry for nootkatone synthesis. Wittig reaction on **63**, followed by oxidation gave the enone **64** which was transformed to (±)-nootkatone (**11**)[48] by a regioselective ring expansion of the cyclopentanone ring.

A final synthesis which gave natural nootkatone (**11**) was reported by Yoshikoshi and co-workers.[49] The diastereomeric ketones **66** which were prepared by a five-step sequence from (-)-β-pinene (**65**), was subjected to methylation and ozonolysis to give a 3:1 mixture of diketones **67** and **68**. In the methylation step, the reaction occurred exclusively from the face anti to the gem-dimethyl

bridge. The mixture of diketones was separated and the major isomer **67** was cyclized with concomitant opening of the cyclobutane ring to afford **69**. The latter compound was dehydrochlorinated to give a 9:1 ratio of (+)-nootkatone (**11**) and (-)-isonootkatone (**12**).[49]

Although eremophilone (**2**) was the most well known member and oldest of the group, it was not until 1974 that the first successful synthesis was reported by Ziegler and Wender.[50] Subsequently, the groups of McMurry,[40] Ficini[51] and Naf,[52] have all reported on their syntheses of this compound. Each of these groups used different strategies to control the stereochemistry of the three chiral centers of eremophilone (**2**).

In the Ziegler-Wender synthesis,[50] 3,4-dimethyl-2-cyclohexen-1-one (**70**) was subjected to conjugate addition with lithium divinylcuprate to afford the unsaturated ketone **71**. The <u>cis</u> disposition of the vicinal methyl groups was assured by the well established preference for such conjugate additions to occur <u>trans</u> to a substituent at C-4 of the cyclohexenone ring. After conversion of **71** to the vinyl-ether **72**, a Claisen rearrangement was planned in the hope of generating the third chiral center at C-7 of eremophilone (**2**) in a stereoselective fashion. It was observed that a mixture of two diastereomers were produced in a 55:45 ratio, the minor isomer **73** being the required

product. After separation, the minor isomer **73** was transformed into (±)-eremophilone (**2**), proceeding *via* the intermediate enone **74** by a 1,3-carbonyl transposition.

Subsequently, Ziegler and co-workers[53] have developed an alternative synthesis with improved stereoselectivity for controlling the stereochemistry of the isopropenyl side chain at C-7. This synthesis started with the unsaturated ester **75** which underwent conjugate addition with lithium diisopropenylcuprate to give a single ester **76** which was converted into the intermediate enone **74**.

The approach used by Ficini and Touzin[51] entailed a conjugate addition of the Grignard reagent **77** to the enone **78** to give stereoselectively the ketone **79**. Conversion of **79** to the alcohol **80** followed by a reduction of the double-bond with lithium in ethylenediamine[54] gave **81** which has the correct relative stereochemistry for eremophilone synthesis.

Naf and co-workers[52] utilized an intramolecular Diels-Alder reaction of the triene-ester **83** which was prepared from ketone **82** by a four-step sequence. The intramolecular Diels-Alder reaction of **83** at 250°C furnished a mixture of *cis*-fused and *trans*-fused adducts **84**. The *trans*-fused adduct was suggested to arise from equilibration of the *cis*-fused isomer during the reaction. Treatment of the mixture of adducts **84** with acid gave the enone **85**. The relative stereochemistry of the three chiral centers were established

in the intramolecular Diels-Alder reaction which was proposed to proceed *via* the transition state **86**. The ketone **85** was converted into the Ziegler-Wender enone **74**, thus completing a formal synthesis of (±)-eremophilone (**2**).[52]

A final approach which resulted in the completely stereoselective formation of the *cis* stereochemistry for the vicinal methyls was successfully applied by the groups of Kitahara,[55] Bohlmann[56] and Yamakawa[57] to the synthesis of some furanoeremophilanes. The approach which was originally reported by Kitahara and co-workers involved an epimerization of the C-4 methyl groups of a decalin derivative such as the ketone **87**. It was observed that treatment of **87** with base afforded the epimeric ketone **88** which has the required *cis* stereochemistry for the vicinal methyls. The transformation of **87** to **88** formed the basis of the synthesis of (±)-eremophilenolide (**19**) and (±)-furano-eremophilane (**6**) by Kitahara and co-workers.[55]

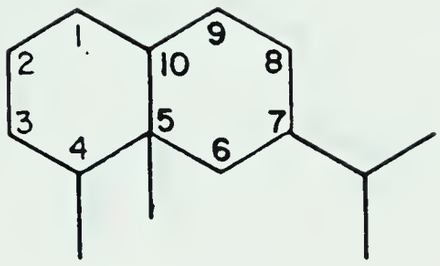
Our interests in the synthesis of eremophilane sesquiterpenes stemmed from some observations acquired from a study of the dienophilicity of 2-carbomethoxy-2-cyclohexen-1-one (**89**)[58] (see Chapter 1). It was observed that the Diels-Alder reactions of enone-ester **89** with 1-substituted and 1,3-disubsituted dienes led to the predominant formation of the adduct that arose from secondary orbital overlap between the diene and the ester

moiety of **89**. For example, its reaction with trans-piperylene at -78°C and under stannic chloride catalysis gave a 5:3 mixture of adducts **90** and **91**. The major adduct **90** which has the cis stereochemistry for the three stereocenters was formed by endo addition of the diene to the ester group of **89**. The minor adduct **91** was obtained by endo-addition to the ketone carbonyl group of the enone-ester **89**. It was also observed that addition of trans-2-methyl-1,3-pentadiene to enone-ester **89** under the same reaction conditions led to a mixture of adducts **92** and **93**. In this case an improved stereoselectivity of 13:1 in favor of the adduct **92** resulting from endo addition to the ester group of **89**, was obtained. The enhanced stereoselectivity in favor of the endo to ester addition, in changing from trans-piperylene to trans-2-methyl-1,3-pentadiene, has been explained by a steric effect (see Chapter 1, Section I).

Based on these observations, a plausible synthetic approach which would allow for the formation of the cis stereochemistry for the vicinal methyl groups, was proposed. Such a proposal depended on the choice of a suitable diene as depicted by structure **94**. The R group in the diene should satisfy two basic criteria to be useful. Firstly, it should be bulky enough so that its Diels-Alder addition to enone-ester **89** would proceed predominantly via transition state **95a** (Scheme IV) to give the adduct **95**,

resulting from addition of diene endo to the ester group of **89**. Secondly, the R group after serving as an element for stereochemical control, should be easily transformed or removed by simple methods.

To demonstrate the feasibility of this approach, petasitolone (**14**) was chosen as the synthetic goal. The results of this study, culminating in a first total synthesis of petasitolone (**14**) will be discussed in the second chapter of the thesis.



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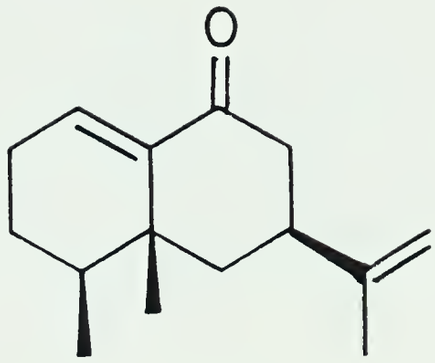

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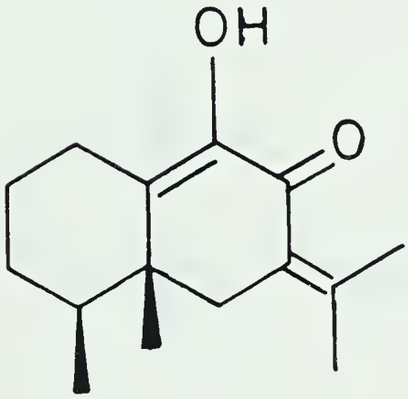

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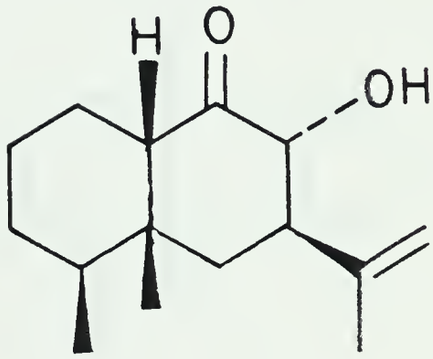

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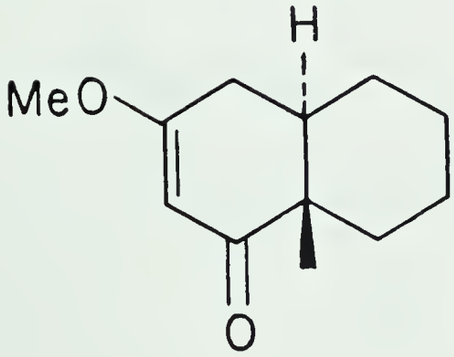

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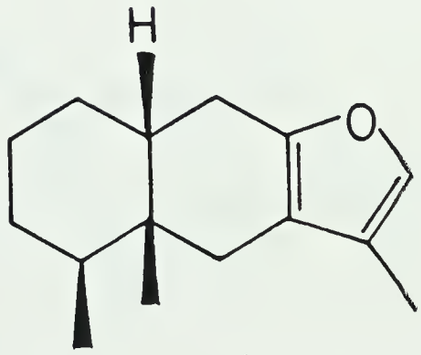

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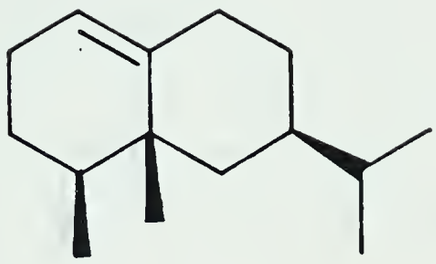

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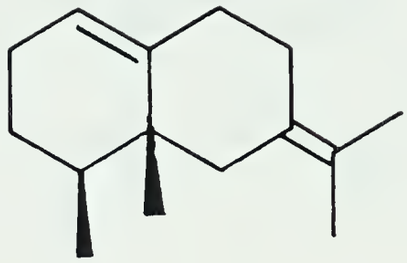

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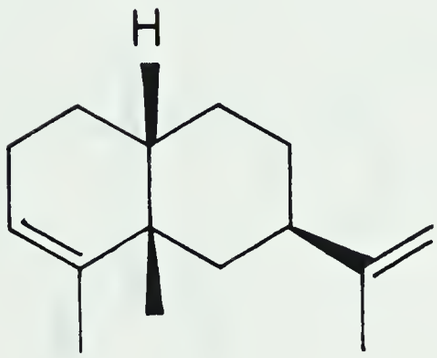

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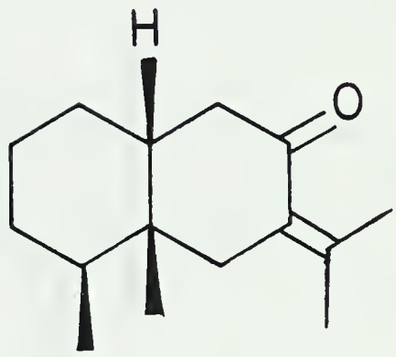

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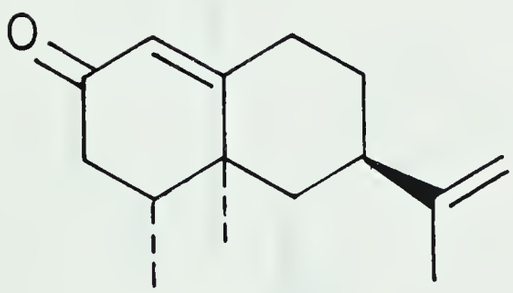

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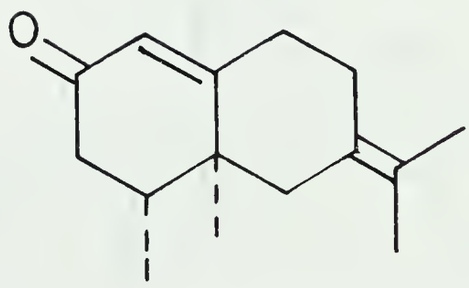

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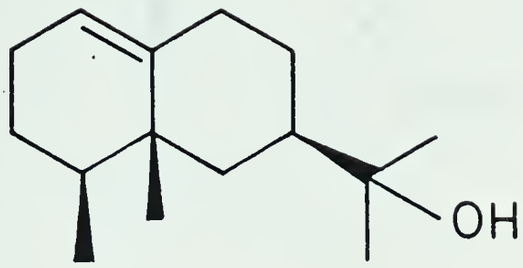

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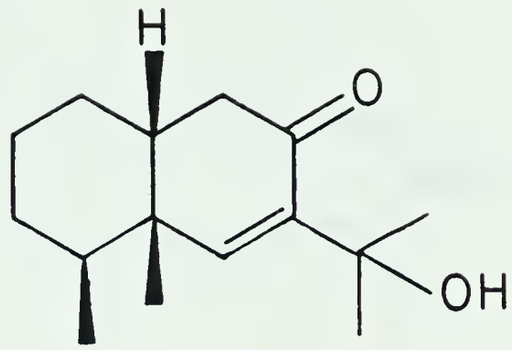

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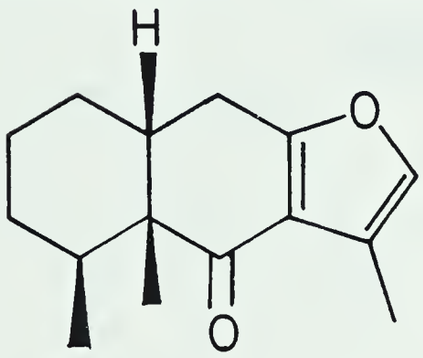

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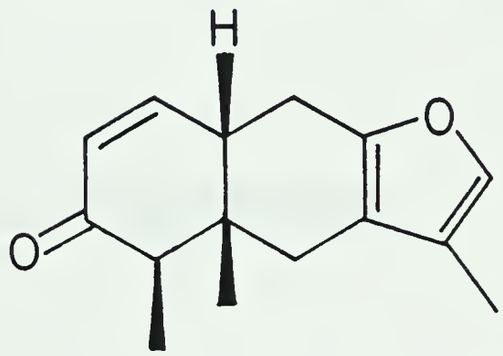

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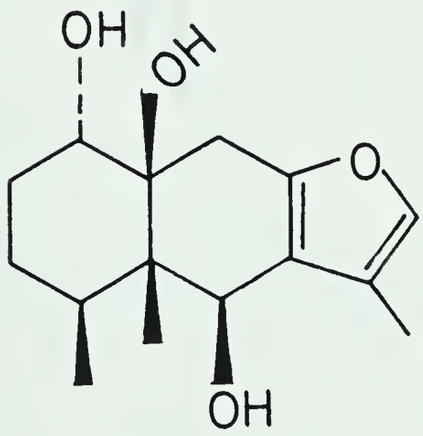

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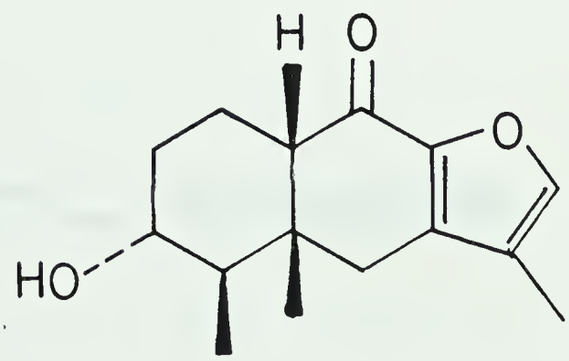

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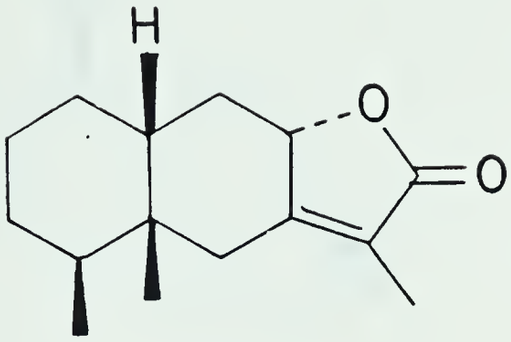

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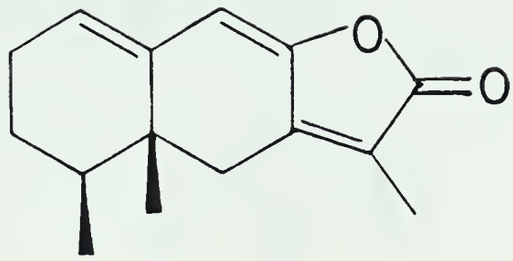

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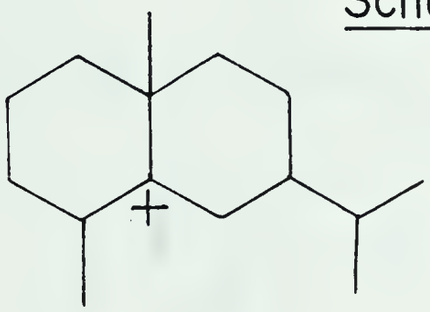

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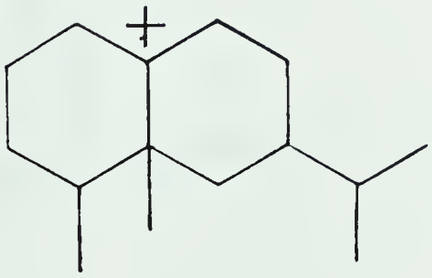

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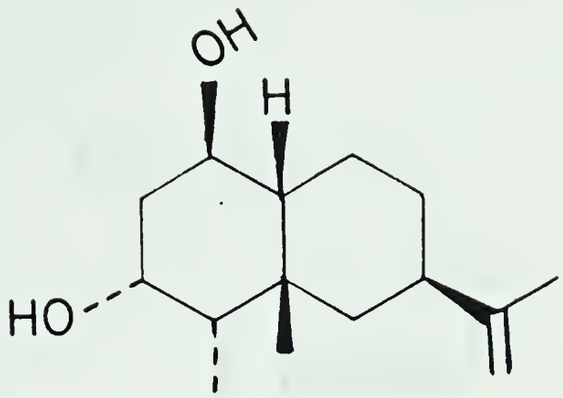

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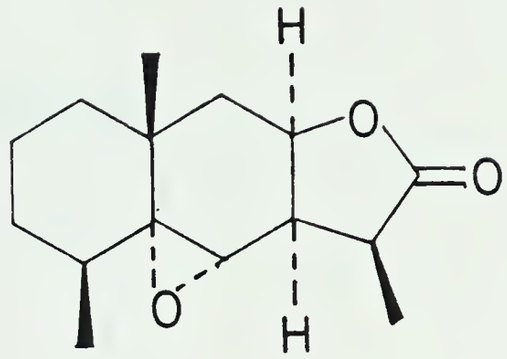

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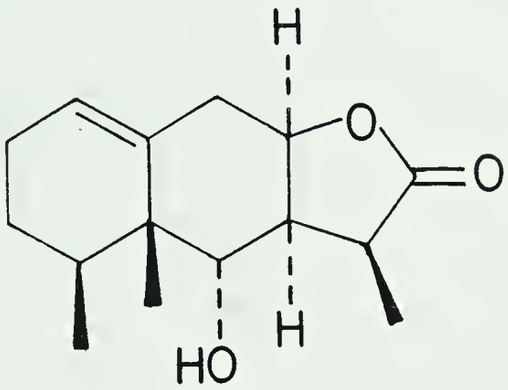

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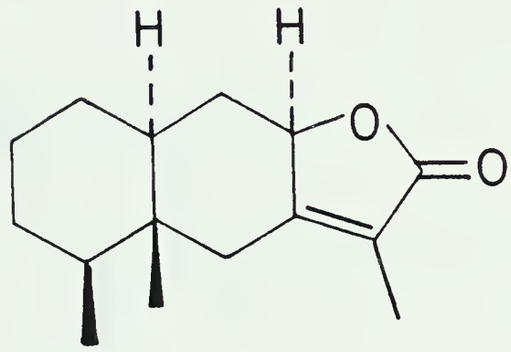

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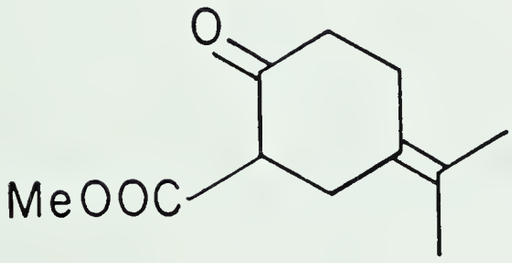

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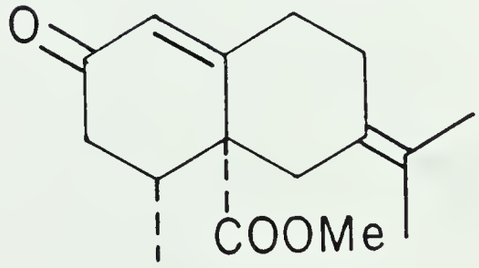

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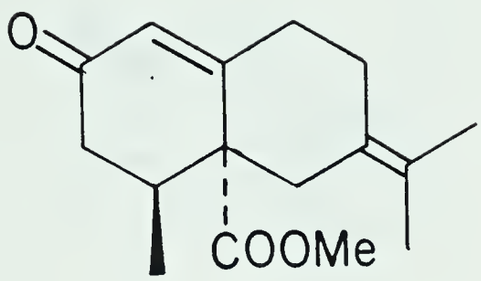

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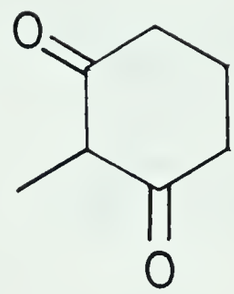

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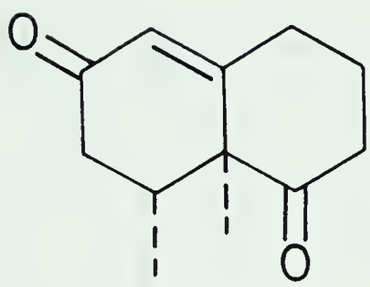

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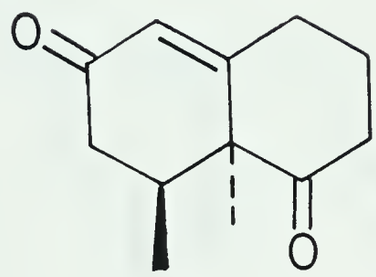

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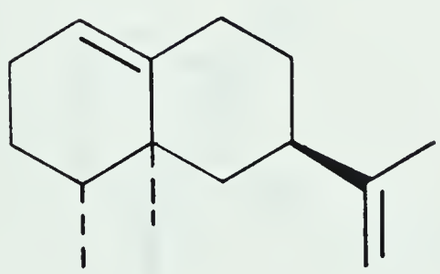

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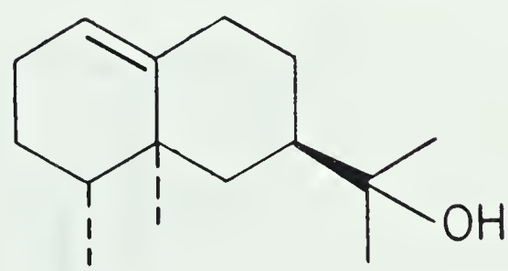

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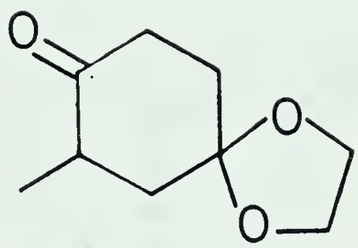

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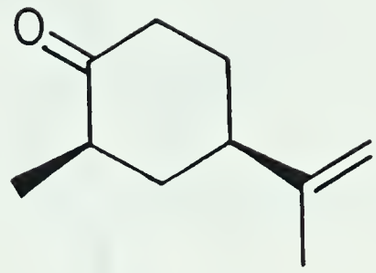

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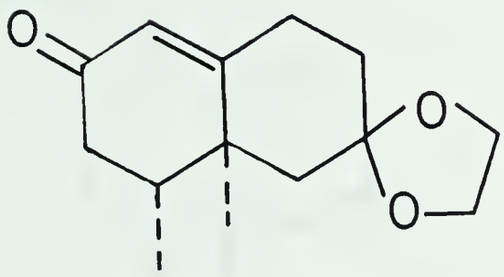

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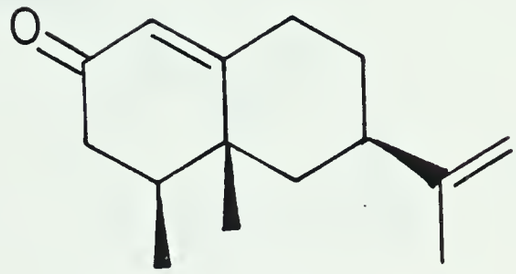

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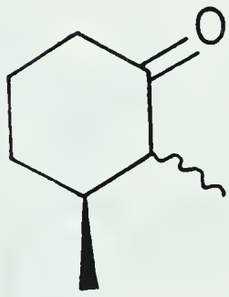

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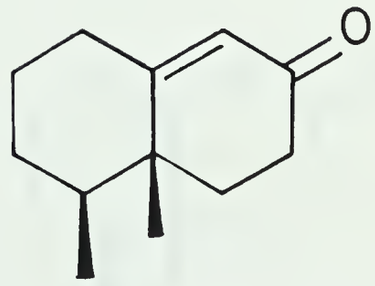

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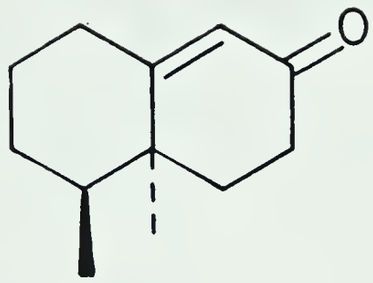

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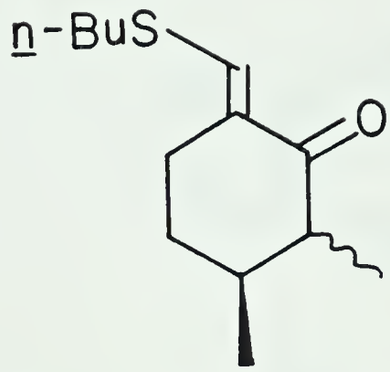

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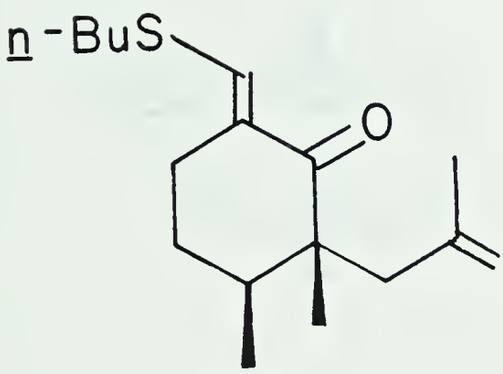

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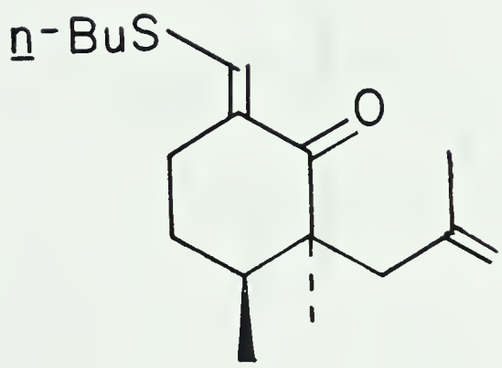

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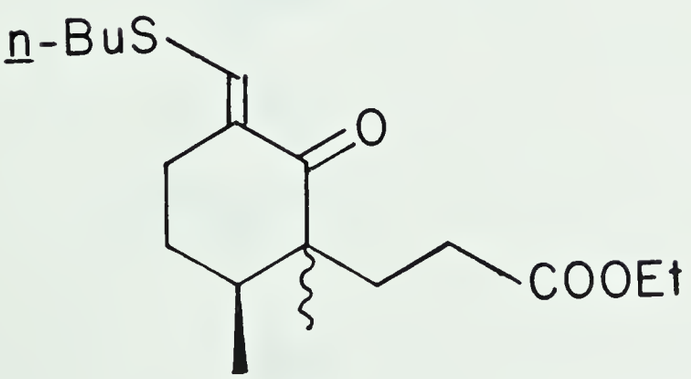

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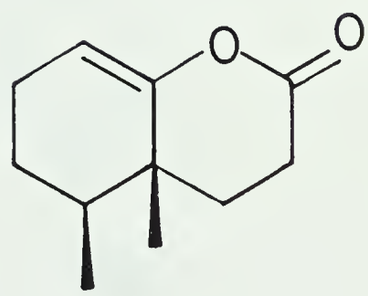

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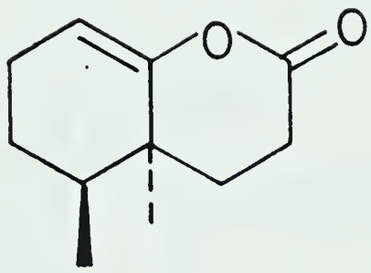

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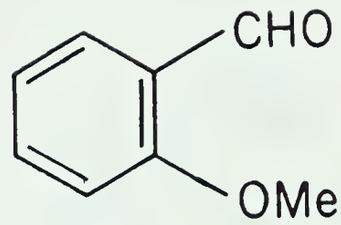

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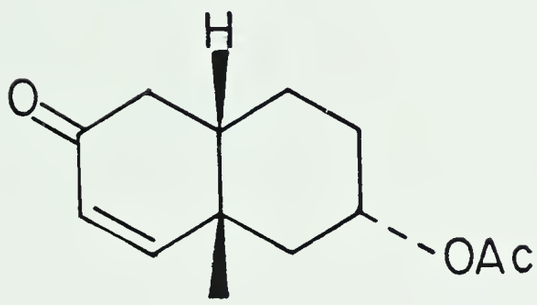

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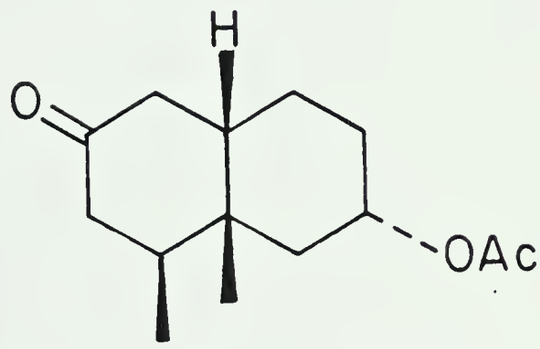

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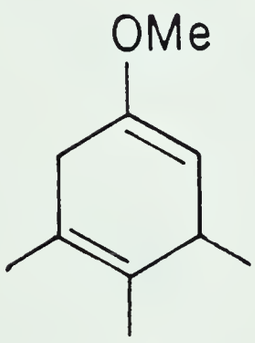

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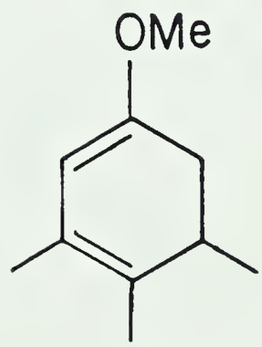

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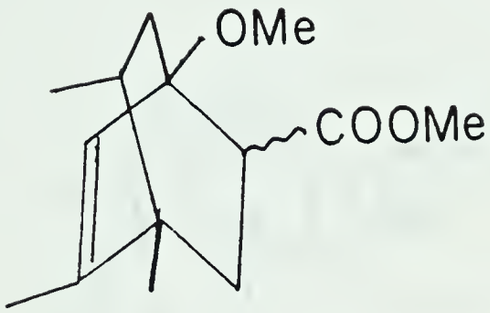

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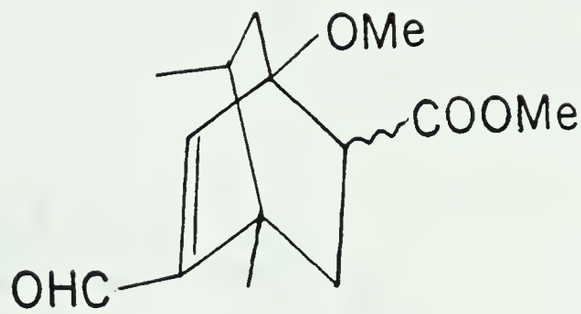

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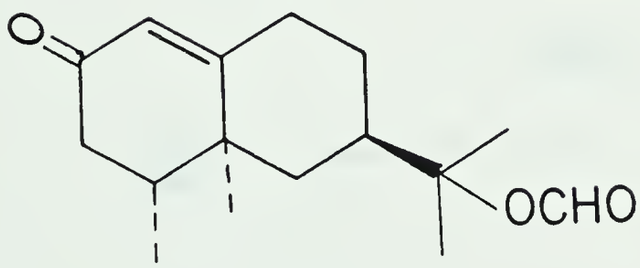

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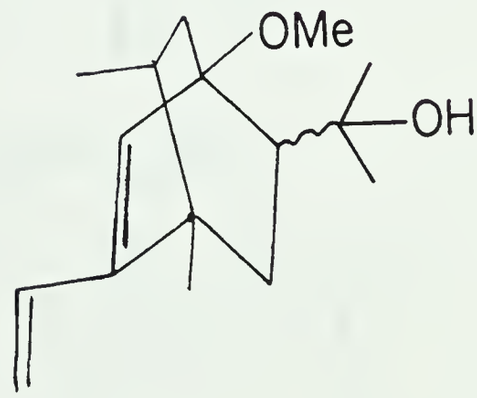

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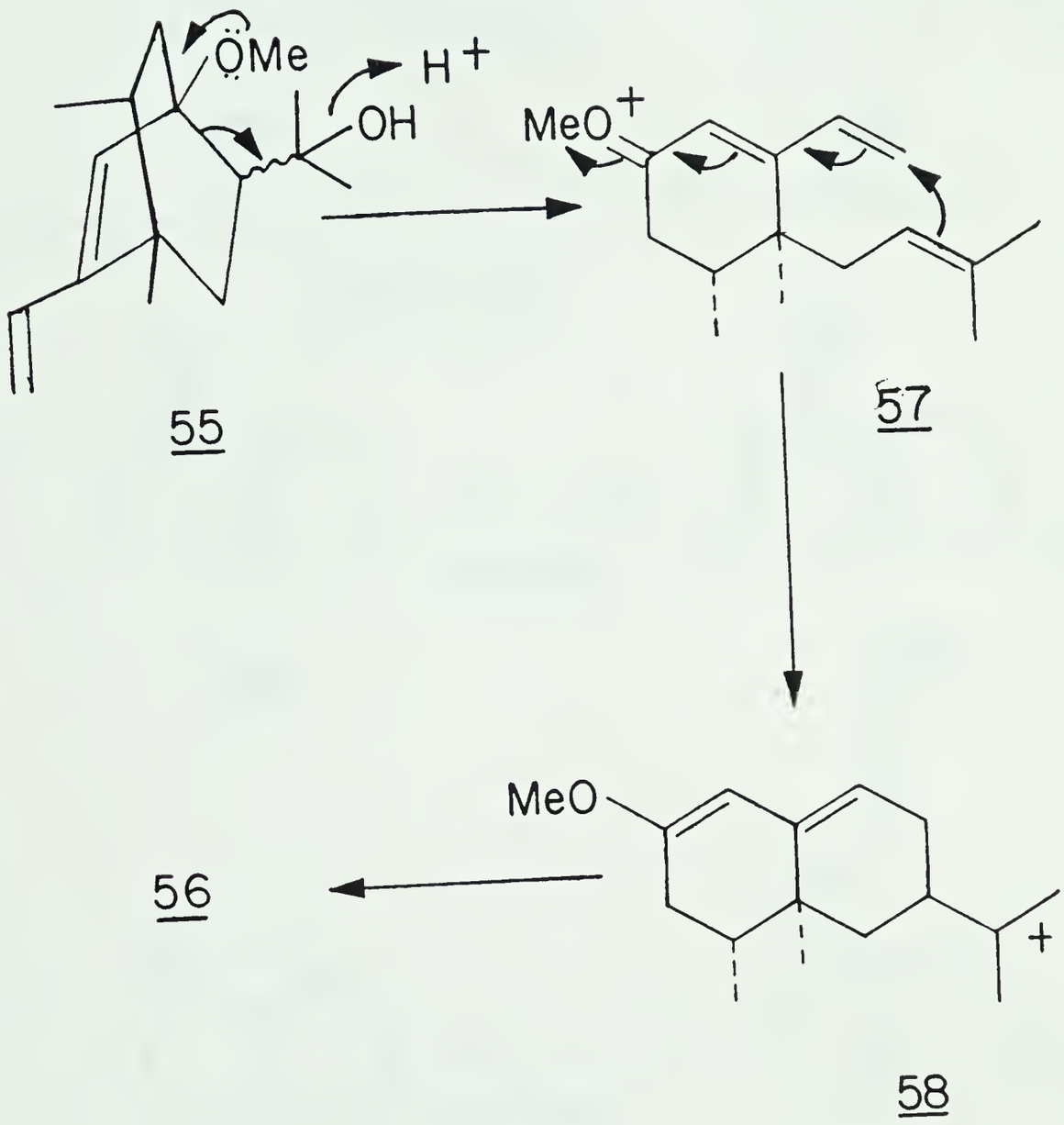
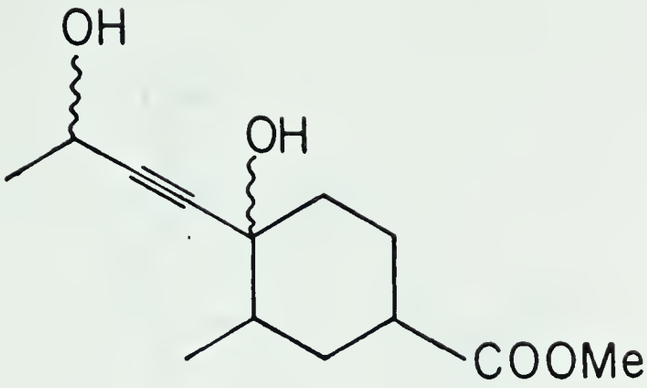
Scheme II





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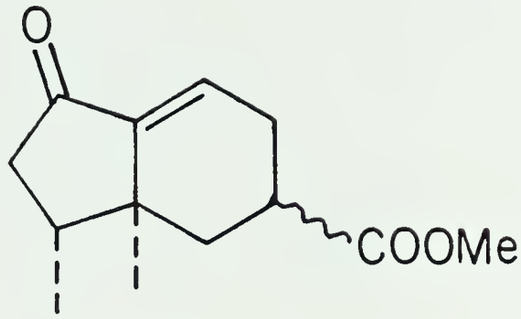

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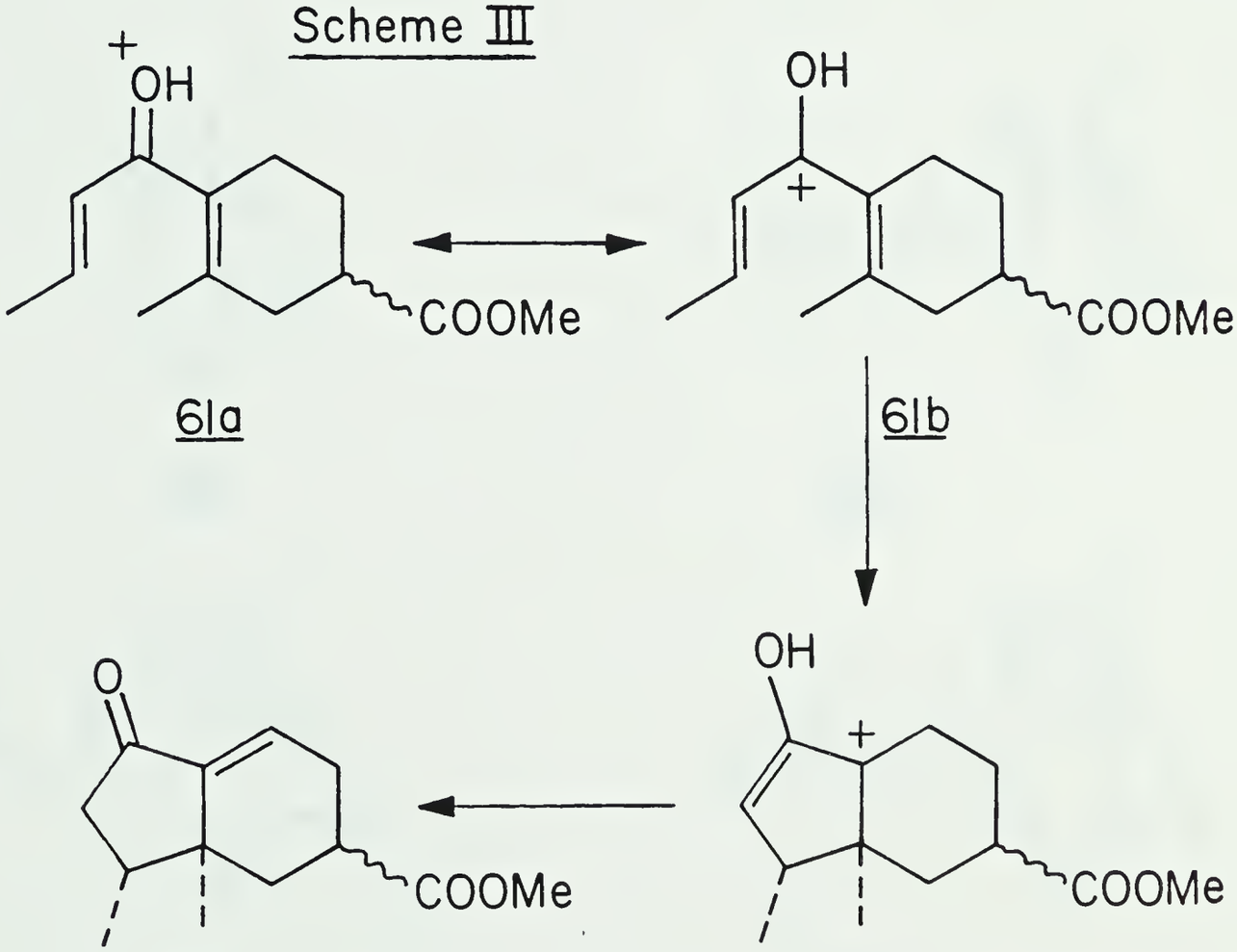

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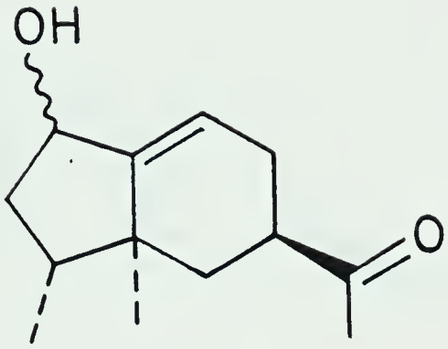

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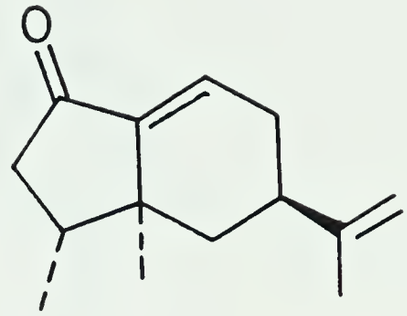

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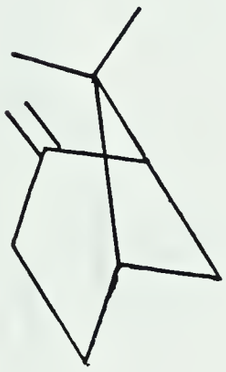

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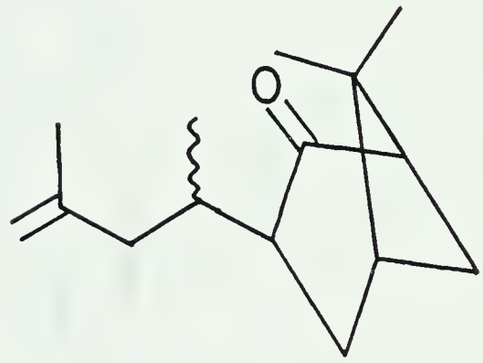

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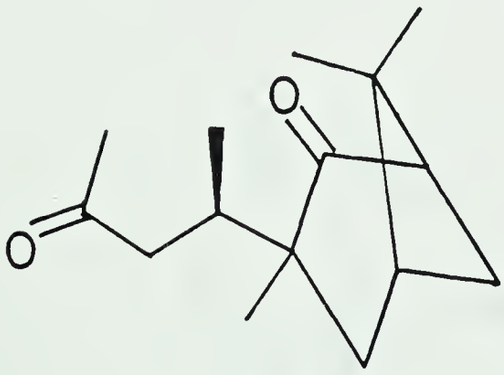

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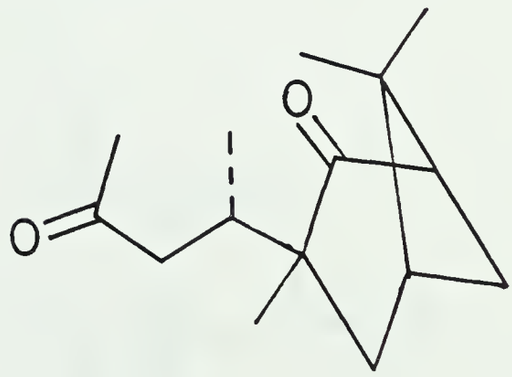

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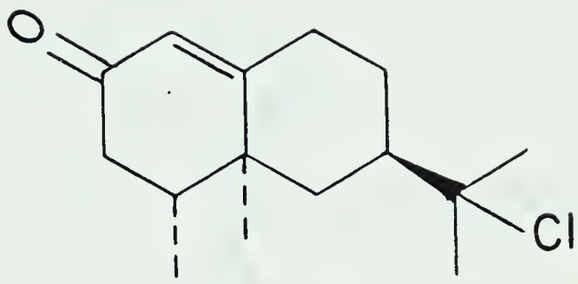

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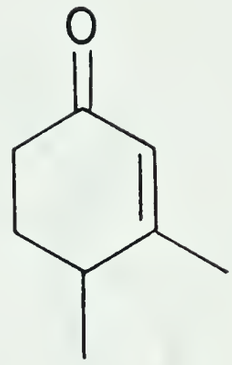

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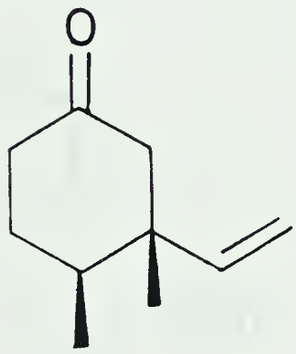

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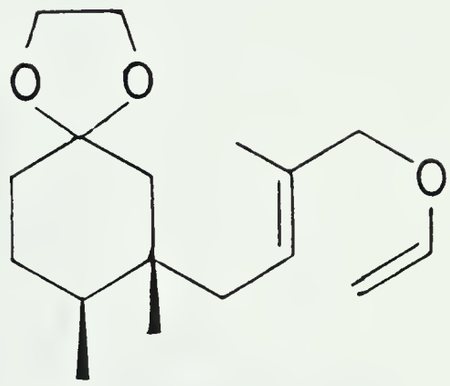

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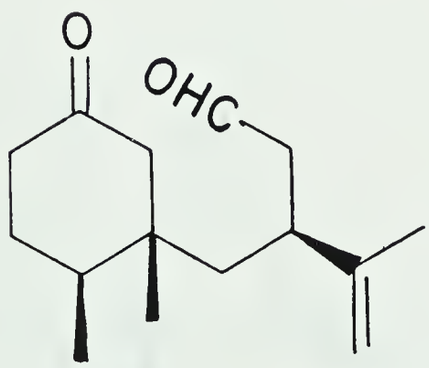

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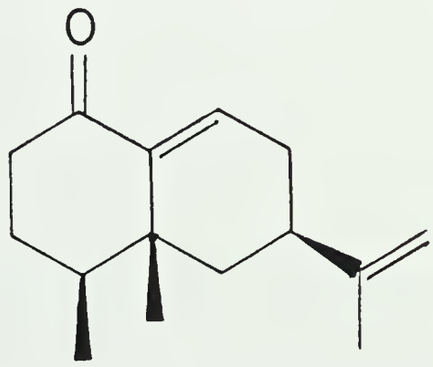

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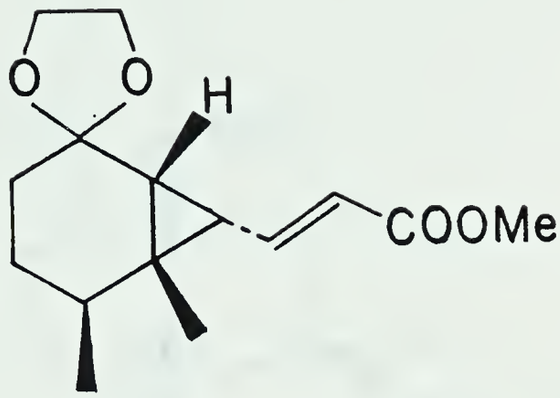

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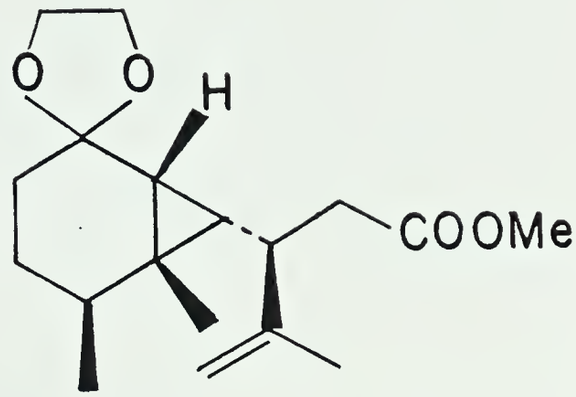

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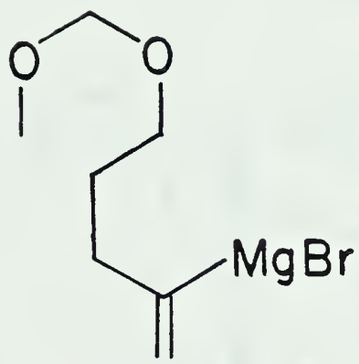

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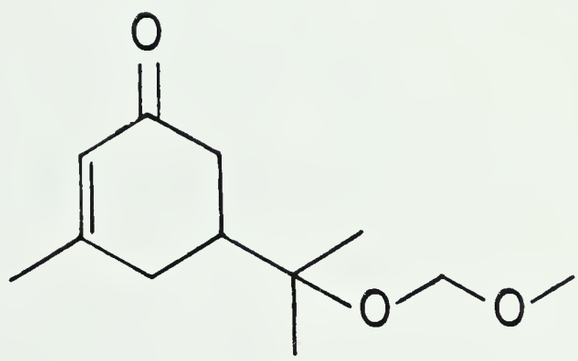

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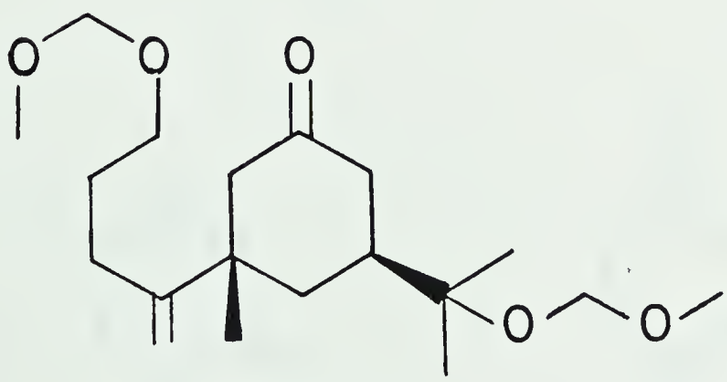

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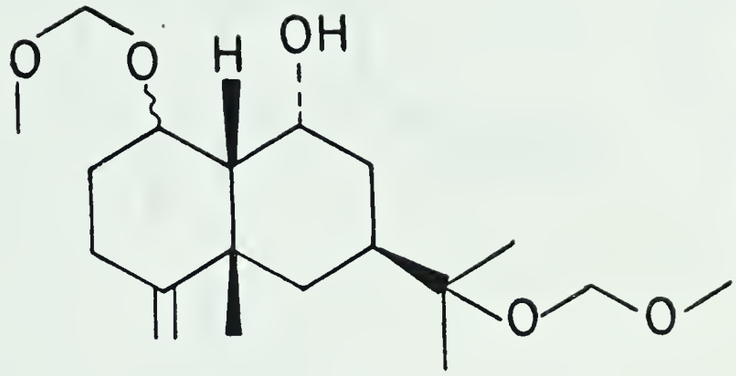

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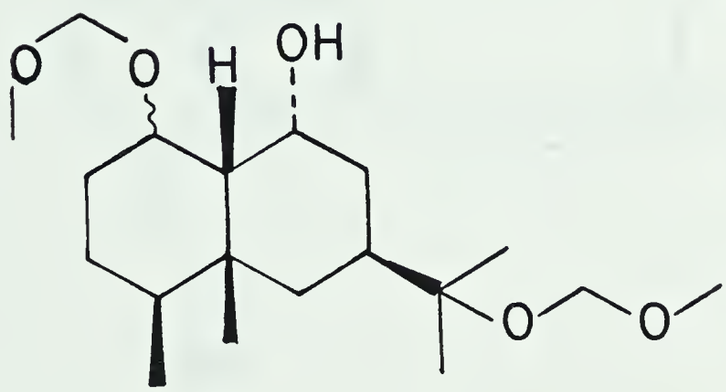

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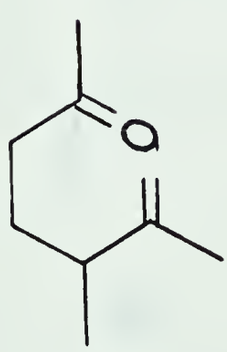

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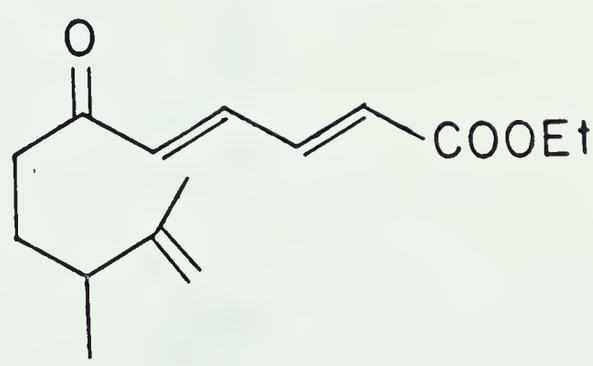

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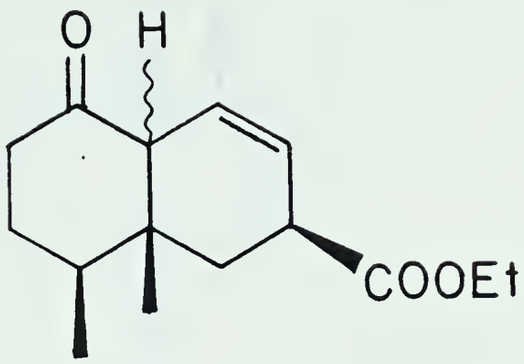

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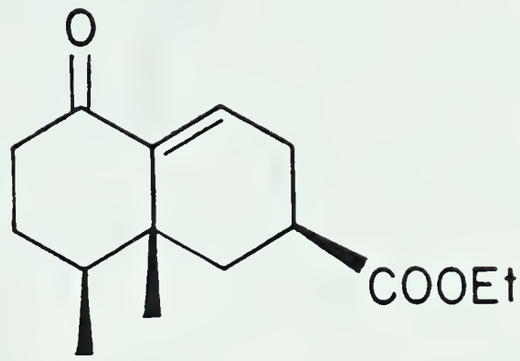

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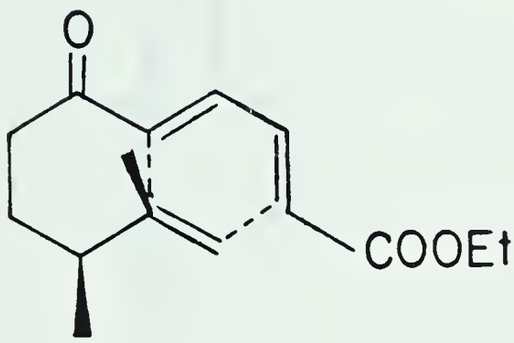

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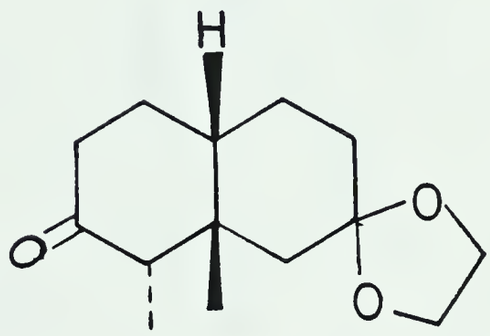

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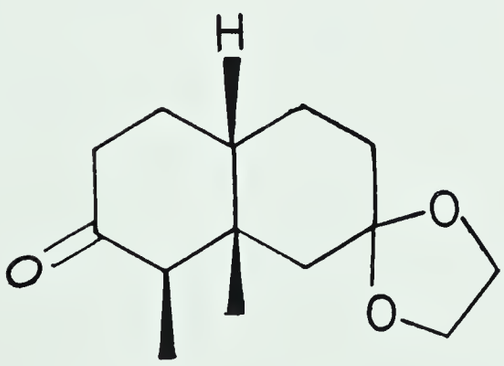

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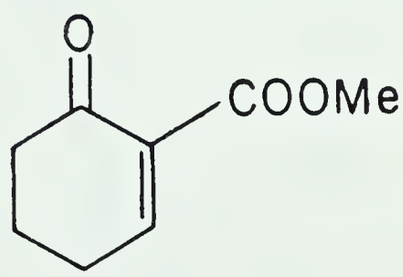

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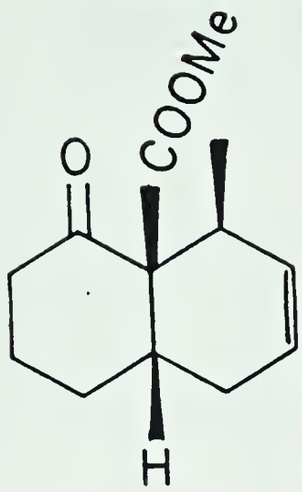

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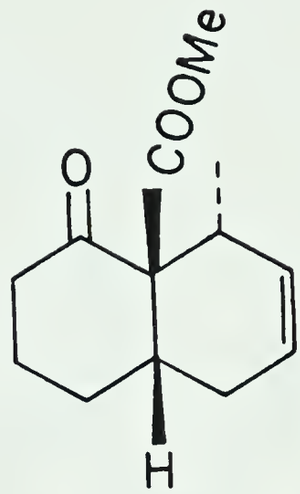

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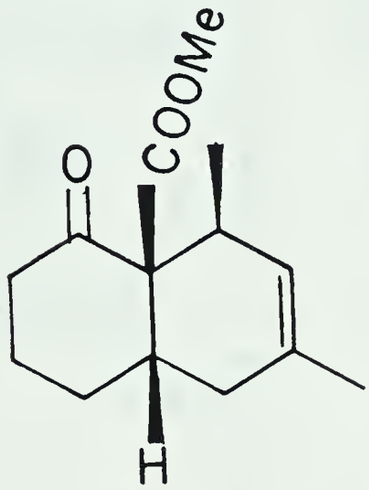

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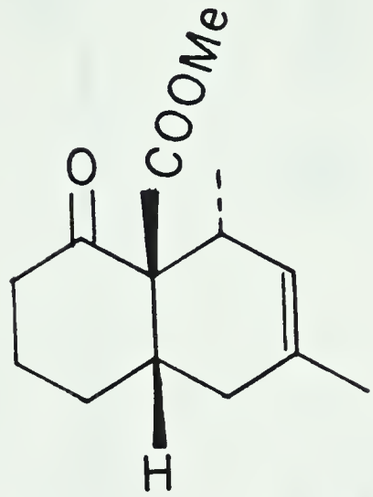

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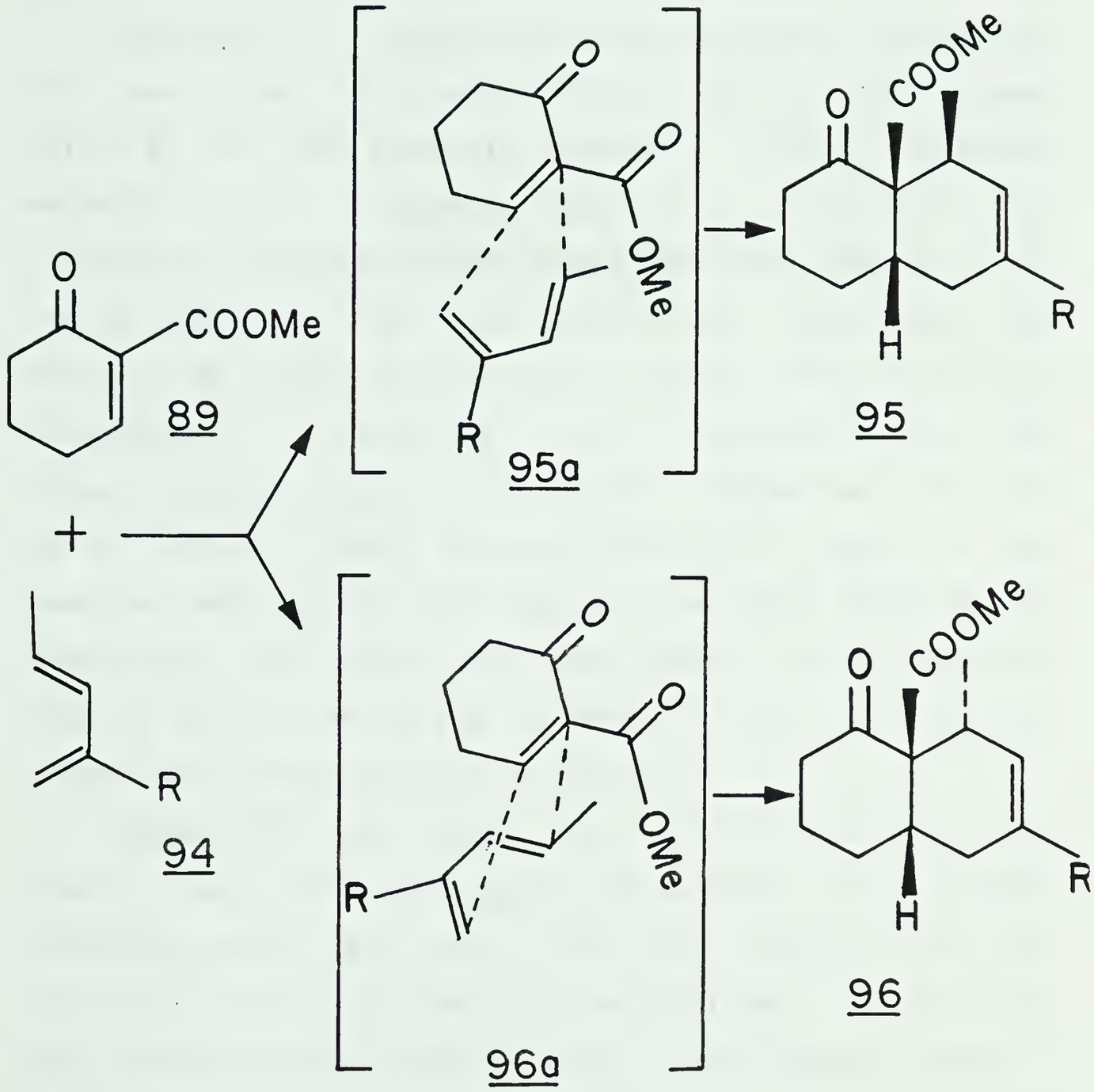
Scheme IV



Results and Discussion

Initially, trans-2-trimethylsilyloxy-1,3-pentadiene (**97**) was chosen for the Diels-Alder reaction with enone-ester **89** for the following reasons. Firstly, different methods[59] are available for the preparation of trimethylsilyloxy-subsituted dienes and these methods can be easily adapted to the preparation of **97**. Such dienes are known to be highly reactive and can react with a variety of dienophiles.[59] Secondly, it is expected that the trimethylsilyloxy group will provide a large steric bulk so as to effect a high stereoselectivity in favor of the required addition of diene endo to the ester group of **89**. Furthermore, the silyl enol ether moiety of the expected adducts **98** can be easily converted[60] into the versatile ketone group which can then be removed.

Diene **97**[61] was easily prepared by generating the kinetic enolate[62] of trans-3-penten-2-one with lithium diisopropylamide at -78°C and then, reaction of the resulting enolate with chlorotrimethylsilane. In this way, the diene was obtained consistently in about 40-60% yield.

The reaction of an ethereal solution of enone-ester **89** and the diene **97** proceeded at -30°C and under stannic chloride catalysis to give a 45% yield of the adducts **99** and

100* in a ratio 3.3:1. Hydrolysis of the labile silyl enol ether moiety of the initially formed adducts **98** occurred during the work-up.

To further optimize the yield and stereoselectivity of the required adduct **99**, various reaction conditions were explored. Two sets of reaction conditions which gave improved stereoselectivity were the use of ether at -50°C which gave a 37% yield of diketones in an improved ratio of 7:1 in favor of **99**, as well as the use of a mixture of ether and methylene chloride (1:1) as solvent at -50°C. In the latter case, it gave a 46% yield of adducts, again in a ratio of 7:1.

Conversion of the major adduct **99** to the corresponding keto-ester **101**, which is required for petasitolone synthesis, was achieved as follows. The 7:1 mixture of diketones was transformed into the thioketals **103** by treatment with 5 equivalents of 1,2-ethanedithiol and 1 equivalent of boron trifluoride etherate in methylene chloride at 0°C for 30 min. Selective monothioketalization of the sterically less hindered ketone carbonyl was thus achieved and a 7:1 mixture of thioketals **103** was obtained in 90% yield. The monothioketal formation was confirmed by the appearance of a four-proton multiplet at δ3.30 in the ^{1}Hmr

*For a discussion of the spectral data and structural assignments, see Chapter 1, Section G.

spectrum and the presence of ir absorptions at 1740 and 1713 cm^{-1}. It was later shown by a subsequent transformation that the thioketalization occurred on the ketone carbonyl at C-6.

Desulfurization of the mixture of thioketals **103** was achieved with Raney nickel (grade W-2) in refluxing ethanol. After chromatographic separations, two products in a ratio of 7:1 in combined yield of 69% were obtained. The major product was found to be identical in spectral properties (^{1}Hmr and ir), as well as TLC behaviour to the keto-ester **101** reported previously (see Chapter 1, Section E). The minor product was also found to be identical to the keto-ester **102** obtained previously (see Chapter 1, Section E).

Although the required keto-ester **101** could be obtained easily and rapidly in moderate yield, we have decided to examine the Diels-Alder reaction of enone-ester **89** with other dienes with the objective of improving the yield of keto-ester **101**. Attempts to prepare the dienes **104** - **107** were not successful. However, when the kinetic enolate[62] of trans-3-penten-2-one was reacted with diethylchlorophosphate at -78°C, the phosphate-diene **108** was obtained in 44% yield. The diene **108** is unusually stable and can be purified by silica gel chromatography.

When enone-ester **89** was reacted with 1.5 equivalent of diene **108*** in ether at -30°C and under stannic chloride catalysis, a 6:1 mixture of **109** and **110**** was obtained in 66% yield. Other reaction conditions such as the use of lower reaction temperatures and other solvents were also employed with a view of improving the stereoselectivity and the yield of adduct **109**. However, experimental results indicated that these reaction conditions were inferior. For instance, when the reaction was done at -78°C, a lower yield of 45% and a similar stereoselectivity of 6:1 were obtained. When the reaction was done in methylene chloride as the solvent*** at -30°C, a 50% yield of adducts **109** and **110**, again in a ratio of 6:1 was obtained.

Conversion of the adduct **109** to the required keto-ester **101** for the petasitolone synthesis, was accomplished as follows. Treatment of the 6:1 mixture of enol-phosphates **109** and **110** with Adam's catalyst at one atmosphere of

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*It is worth noting that very few phosphoryloxy-substituted dienes have been used in Diels-Alder reactions. The only known example is the phosphate-diene derived from methyl vinyl ketone.[63,64]

**For a discussion of the spectral data and structural assignments, see Chapter 1, Section H.

***The use of ether led to the formation of a cloudy white solution while the use of methylene chloride gave a clear solution. These observations could be due to the different solubilities of the Lewis acid complexes with the reactants and/or products. The higher yield of adducts obtained makes ether the solvent of choice in this Diels-Alder reaction.

hydrogen pressure resulted in the reductions of the double-bond as well as the phosphate group[65,66] to give the chromatographically separable keto-esters **101** and **102** in 87% combined yield.

At this stage, it is worth noting that three different routes converging on the keto-ester **101** were developed. The use of trans-piperylene, trans-2-trimethylsilyloxy-1,3-pentadiene (**97**) and the phosphoryloxy-substituted diene **108** for the Diels-Alder reactions with enone-ester **89** led to the preferential formations of the adducts **90**, **99** and **109** respectively. These adducts were subsequently converted to the keto-ester **101**. Of these three routes to **101** the least efficient was the use of trans-piperylene as the diene while the use of the more bulky diene **95** led to higher stereoselectivity and better yield. The best method for the preparation of the keto-ester **101** in high yield was the use of the more stable diene **108** for the Diels-Alder reaction with enone-ester **89**.

The use of the keto-ester **101** for the synthesis would require a conversion of the carbomethoxyl group into a methyl substituent. Results of previous studies[67,68] indicated the feasibility of this transformation. It involved the initial conversion of the ester group to a hydroxymethylene moiety. The resulting hydroxyl group was then converted to a derivative which could be reduced

without steric interference from the adjacent neopentyl center. It has been shown[69] that tetramethyl phosphorodiaminate[70] (TMPDA) derivatives of alcohols can be reduced to hydrocarbons with lithium in ethylamine/tetrahydrofuran/t-butanol. Such TMPDA derivatives of sterically hindered alcohols are, however, difficult to prepare directly from reaction of the alcohol with tetramethyl phosphoramidic chloride. This difficulty can be circumvented[71] by conversion of the alcohol first to the dimethyl chlorophosphoramidate derivative using dimethylphosphoramidic dichloride followed by treatment of the resulting intermediate with dimethylamine to give the TMPDA derivative.

Inherent in this sequence of reactions was the necessity of protection of the ketone carbonyl of **101**. Accordingly, ketalization was attempted. Repeated treatments of keto-ester **101** in ethylene glycol with a catalytic amount of p-toluenesulfonic acid in refluxing benzene led to the recovery of the starting material. None of the ketal **111** could be isolated. This lack of reactivity was in contrast to the ketalization of **112** which readily gave a 96% yield of the ketal **113**.[67]

However, it was found that the thioketalization of **101** could be achieved; albeit the reaction was rather sluggish and only moderate yield of product was obtained. Thus,

treatment of the keto-ester **101** with one equivalent of boron trifluoride etherate in 1,2-ethanedithiol as the solvent at 0°C for 3 days, gave the thioketal **114** in 48% yield. The thioketal **114** showed an ir absorption at 1725 cm^{-1} for the ester carbonyl and gave a molecular ion peak at m/e 300.1216 in the mass spectrum, confirming its chemical formula as $C_{15}H_{24}O_2S_2$. The ^{1}Hmr spectrum displayed a multiplet at δ3.15 for the four protons of the ethylene thioketal moiety. A methyl ester singlet appeared at δ3.68 and the secondary methyl showed a doublet at δ1.31. These spectral data are in agreement with the structure **114** for the thioketal.

Unfortunately, treatment of the thioketal **114** with different reducing agents either led to the recovery of starting material ($LiAlH_4$) or intractable mixture of products ($LiEt_3BH$ and $Na(CH_3OCH_2CH_2O)_2AlH_2$).

The unexpected difficulties associated with the protection of the ketone carbonyl as well as the reduction of the ester group led us to explore an alternative route for effecting the required transformation of the carbomethoxyl group to an angular methyl substituent. It was decided that the keto-ester **101** could be converted into the diol **115** in which the primary and secondary alcohol groups would have different reactivity and thus, selective reactions could be performed.

Treatment of an ethereal solution of keto-ester **101** at 0°C with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) gave a single crystalline diol (m.p. 97-99°C) in 96% yield. The presence of 12 lines in the ^{13}Cmr spectrum indicated that only one isomer was formed in the reduction. In the mass spectrum, a peak at m/e 180.1517 of 42% intensity corresponded to the M^+-18 peak. Such characteristic peak of M^+-18 in the mass spectrum of alcohol is well documented.[72] The ir spectrum showed hydroxyl absorption at 3317 cm^{-1}. The formation of a diol was confirmed by the presence of two signals at δ2.74 and 2.26 in the ^{1}Hmr spectrum which disappeared on deuterium exchange with D_2O. ^{1}Hmr signals also appeared at δ4.35 and 3.71 as doublets with coupling constants of 12 Hz each. These signals were assigned to the two methylene protons of the angular hydroxymethylene group.

Assuming that attack of the reducing agent occurred from the less hindered convex face of the cis decalin system of the keto-ester **101**, then the resulting diol would have the relative stereochemistry as shown in structure **115** in which the proton adjacent to the secondary hydroxyl group would be axial. This was confirmed by the presence of a signal at δ3.83, due to the proton adjacent to the secondary hydroxyl group. This signal appeared as a doublet of doublets with a large diaxial coupling constant of 14 Hz and

a smaller axial-equatorial coupling constant of 6.0 Hz. This assignment was however, of no consequence to the synthesis, as subsequent reactions would destroy this asymmetric center.

As expected, selective mesylation of the primary hydroxyl group of **115** could be achieved. When the diol was reacted with one equivalent of methanesulfonyl chloride and excess pyridine in methylene chloride at -20°C, the mono mesylate **116** was obtained. It was found to be contaminated by a small amount (~10%) of the regioisomeric monomesylate **117***. The mesylate **116** showed ir adsorption, at 3315 cm^{-1} due to the presence of an alcohol. The ^{1}Hmr spectrum displayed signals at δ4.73 and 4.48 as doublets, as well as a multiplet at δ3.68 for the proton adjacent to the hydroxyl group. Methyl signals appeared at δ3.08 as a singlet and at δ1.01 as a doublet. A downfield shift observed for the two methylene protons of the angular substituent from δ4.35 and 3.71 in the diol **115** to δ4.73 and 4.48 in the mesylate **116** confirmed that the primary alcohol was mesylated.

The reason for the introduction of the mesylate group to the primary alcohol was due to its known reduction to the

*Closer examination of the high field ^{1}Hmr spectrum (400 mHz) of the purified product indicated this contamination by the mesylate **117**: δ4.83 (dd, 1H, J = 13 Hz, J' = 4.5 Hz, -CH-O-), 3.91 (d, 1H, J = 12 Hz, -CHH-OH), 3.88 (d, 1H, J = 12 Hz, -CHH-CH), 3.04 (s, 3H, $-OSO_2CH_3$) and 0.90 (d, 3H, J = 7.0 Hz, $-CH-CH_3$).

corresponding alkane.[73,74] The reduction was not done until the oxidation of **116** to the keto-mesylate **118** using Jone's reagent was carried out. The oxidation furnished **118** in about 60-77% yield after chromatographic purification. The appearance of a band at 1703 cm^{-1} in the ir spectrum indicated that a ketone was formed. In the mass spectrum, a molecular ion peak at m/e 274.1233 was observed, characteristic for the chemical formula $C_{13}H_{22}O_4S$. The ^{1}Hmr spectrum displayed signals at δ4.70 and 4.33 as doublets for the two methylene protons of the angular substituent. A methyl singlet appeared at δ3.05 and a methyl doublet appeared at δ0.68. The spectral data were in accord with the assignment of structure **118** to the oxidized product.

Reduction of the mesylate group of **118** would lead to ketone **119**, an advanced intermediate with the required all cis relative stereochemistry for petasitolone synthesis. This reduction was done, employing the reported conditions of a mixture of excess zinc dust and sodium iodide in refluxing 1,2-dimethoxyethane.[74] No detectable reaction (as indicated by TLC) was observed, even after prolonged heating. It was however observed that changing to a higher boiling solvent led to the disappearance of the starting material. Thus, reaction of a mixture of keto-mesylate **118**,

zinc dust and sodium iodide in refluxing N,N-dimethylformamide* furnished two products in a combined yield of 81%.

The products were easily separated and purified by column chromatography. The less polar compound was obtained as a colorless oil in 60% yield. It showed ir absorption at 1706 cm^{-1}, characteristic of a ketone. A molecular ion peak at m/e 180.1515 in the mass spectrum indicated the chemical formula as $C_{12}H_{20}O$. These spectral data together with the appearance of a new methyl singlet at δ1.08 in the ^{1}Hmr spectrum indicated that it was the required ketone **119**.

The more polar product was obtained in 21% yield. The ir spectrum of this product showed the presence of an alcohol (3443 cm^{-1}) and the absence of carbonyl absorptions. A molecular ion peak at m/e 180.1521 in the mass spectrum indicated the isomeric nature of this product to the ketone **119**. The ^{1}Hmr spectrum showed a methyl doublet at δ1.07, as well as two doublets at δ0.69 and 0.25,

*Mechanistically, it would be unlikely for the reduction to proceed *via* an SN_2 displacement of the highly hindered neopentyl mesylate group by iodide. To explore the possibility of an SN_2 displacement, keto-mesylate **118** was refluxed in N,N-dimethylformamide in the presence of sodium iodide alone. After 47 h the starting material was recovered. Furthermore, treatment of the keto-mesylate **118** with zinc in refluxing N,N-dimethylformamide or in refluxing acetic acid gave no detectable reactions as indicated by TLC. These results seemed to suggest that a mixture of zinc dust and sodium iodide was necessary for the reduction of the neopentyl mesylate group of **118**.

each due to a single proton and each with coupling constant of 5.5 Hz. Based on these spectral data, the minor product was assigned to the cyclopropanol **120**. This assignment was further supported by its subsequent conversion to the ketone **119**. Thus, treatment of the cyclopropanol **120** with aqueous sodium hydroxide in refluxing N,N-dimethylformamide furnished the ketone **119** in 48% yield.

The spectral data for **119** was found to be identical in all respects with those of an authentic sample prepared from the published procedure.[75]

With the structure of ketone **119** firmly established, the next stage of the synthesis required the introduction of the isopropyl alcohol moiety as well as some functional groups transformations to the functionalities of petasitolone (**14**).

To introduce a carbomethoxyl group, which would provide a handle for transforming into the isopropyl alcohol moiety at the α-carbon of the ketone of **119**, a mixture of **119**, sodium hydride and dimethyl carbonate was refluxed in benzene. After heating for 50 h a mixture of three products was obtained in 85% yield. The ir spectrum showed a set of bands at 1748, 1702, 1640 and 1604 cm^{-1}, characteristic of the presence of a mixture of keto-enol tautomers of a β-keto ester. The mass spectrum showed a molecular ion peak at m/e 238.1572, corresponding to the chemical formula $C_{14}H_{22}O_3$.

Examination of the ^{1}Hmr spectrum revealed the presence of three sets of signals in an integral ratio of ~5:5:1. It showed a low field singlet at δ12.72, characteristic of an enolic proton. Methyl singlets appeared at δ3.74, 3.73 and 3.70, each due to a methyl ester for the three compounds. The angular methyl signals appeared at δ1.15, 1.11 and 1.05, each as a singlet and the secondary methyl signals appeared at δ0.95, 0.73 and 0.66 as doublets. Based on these spectral data and the nature of the reaction, the mixture of three compounds was assigned with the structures **121**, **122** and **123**. These compounds exist as a mixture of keto-enol tautomers as depicted in Scheme V.

Treatment of the mixture of **121**, **122** and **123** with sodium borohydride in methanol at 0°C for 30 min led cleanly to a chromatographically separable mixture of two epimeric alcohols in a ratio of 3:1 (by ^{1}Hmr integration). The minor alcohol, obtained in 20% yield, showed characteristic alcohol (3480 cm^{-1}) and ester absorptions (1728 cm^{-1}) in the ir spectrum. A molecular ion peak at m/e 240.1720 indicated a chemical formula of $C_{14}H_{24}O_3$ for the product. In the ^{1}Hmr spectrum a methyl ester singlet appeared at δ3.76 while the angular methyl singlet appeared at δ1.00. The signal at δ0.91 appearing as a doublet, was due to the secondary methyl group.

Closer examination of the ^{1}Hmr spectrum has allowed the assignment of the stereochemistry of this reduction product as well. A signal appearing at δ3.62, as a doublet of doublets with coupling constants of 6.0 and 5.0 Hz was assigned to the proton adjacent to the hydroxyl group. Another signal, due to the methine proton on the α-carbon of the methyl ester appeared at δ2.83 as a multiplet. It showed discernable coupling constants of 10 Hz and 5.0 Hz. A third signal due to the hydroxyl proton appeared at δ3.35 as a doublet (J = 6.5 Hz). On deuterium exchange with D_2O, this latter signal disappeared and the signal at δ3.62 collapsed to a doublet with coupling constant of 5.0 Hz. This observation indicated that the proton on the carbon bearing the hydroxyl group was equatorially disposed. Together, with the presence of a diaxial coupling constant of 10 Hz for the signal at δ2.83, it led to the assignment of the structure **124** for the minor alcohol, where the methine proton (at δ2.83) on the α-carbon of the methyl ester would be axial.

The major alcohol, obtained as white crystals (m.p. 82-84°C) in 69% yield, was assigned to the structure **125.** This alcohol showed ir absorptions at 3520 (alcohol) and 1719 cm^{-1} (ester), as well as a molecular ion peak at m/e 240.1723 ($C_{14}H_{24}O_3$) in the mass spectrum. The stereochemical assignments were again made based on the ^{1}Hmr

spectrum. A signal at δ2.73 was assigned to the methine proton on the α-carbon of the methyl-ester. It appeared as a doublet of doublets of doublets with coupling constants of 13, 11, and 4.5 Hz. The presence of two large coupling constants of 13 and 11 Hz indicated that this methine proton was axial and further coupled to two adjacent axial protons. One of these axial protons had to be on the carbon bearing the hydroxyl group. That this was so, was confirmed by the presence of a signal at δ3.53 with coupling constants of 11 and 4.5 Hz assigned to the proton adjacent to the hydroxyl group. On deuterium exchange with D_2O, this signal collapsed to a doublet with coupling constant of 11 Hz and the signal at δ2.46 (J = 4.5 Hz) disappeared. These spectral data supported the assignment of structure **125** to the major product.

A dehydration of the β-hydroxyesters **124** and **125** was required at this stage. It was found that the dehydration could be easily accomplished by treating each alcohol with dicyclohexylcarbodiimide in the presence of catalytic amount of cuprous chloride[76,77] in refluxing N,N-dimethylformamide. Subsequently, it was found that mixtures of alcohols **124** and **125** could be used as well and the unsaturated ester **126** was obtained in about 74-85% yield.

Ester **126** showed a molecular ion peak at m/e 222.1618 ($C_{14}H_{14}O_2$) and ir absorptions at 1717 and 1642 cm^{-1}, due to

the α,β-unsaturated ester moiety. The ^{1}Hmr spectrum displayed methyl signlets at δ3.76 and 1.04. A methyl doublet appeared at δ0.91. A signal appearing as a doublet of doublets at δ6.90 was due to the vinylic proton.

Introduction of an oxygen functionality at the allylic position of **126** was achieved with selenium dioxide oxidation. When **126** was reacted with excess selenium dioxide in refluxing acetic acid for about two days, a product was isolated in 61% yield. Recrystallization from a solution of ether in petroleum ether gave white crystals of pure product (m.p. 119-120°C).

The compound showed a molecular ion peak at m/e 280.1856 corresponding to the chemical formula $C_{16}H_{24}O_4$. The ir spectrum showed bands at 1723 cm^{-1} due to the unsaturated methyl ester and at 1737 cm^{-1} suggesting the presence of another ester. In the ^{1}Hmr spectrum, the appearance of a singlet at δ2.05 and a multiplet at δ5.74 indicated the presence of an acetate group. A singlet at δ7.22 was due to the vinylic proton. The remaining methyl signals appeared at δ3.75 for a methyl ester, at δ1.10 for the angular methyl and at δ0.89 for the secondary methyl group. Based on these spectral data, the structure **127** was assigned to the product of the selenium dioxide oxidation of **126**.

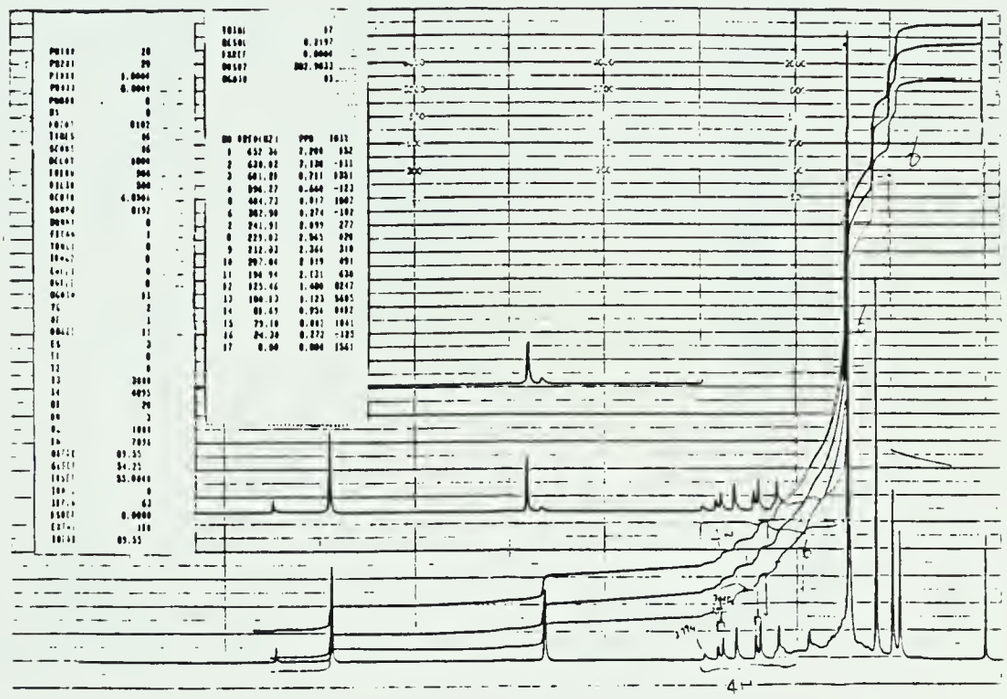
The stereochemistry of the newly created asymmetric center at the carbon bearing the acetate group was determined from the splitting pattern of the signal at δ5.74. This signal for the allylic methine proton showed coupling constants of 4.0 and 1.5 Hz. The small values of these coupling constants was characteristic of the equatorial disposition for this proton. The axial disposition for the acetate group was not surprising since the approach of the active selenium reagent occurred from the less hindered convex face of the cis decalin system of **126**.

The allylic acetate **127** was converted into petasitolone (**14**) as follows. The isopropyl alcohol moiety of **14** was generated by treatment of the allylic acetate **127** with excess methyllithium at -78°C. At the same time, the acetate group of **127** was also removed.

The resulting diol **128** showed ir absorptions at 3480 and 3377 cm^{-1} as well as a molecular ion peak at m/e 238 corresponding to the chemical formula $C_{15}H_{26}O_2$. The ^{1}Hmr spectrum showed a singlet at δ5.74 for the vinylic proton. New methyl signals appeared at δ1.47 and 1.39 as singlets, besides the singlet at δ1.00 and the doublet at δ0.34. The signal at δ4.51, appearing as a doublet of doublets, was due to the allylic methine proton. Two signals at δ2.78 and 2.40 disappeared on deuterium exchange with D_2O.

Final transformation of the diol **128** to petasitolone (**14**) was accomplished by oxidation. Initially, pyridinium dichromate[78] (PDC) was used as the oxidant. Treatment of diol **128** with a slight excess of PDC in methylene chloride for 40 min furnished petasitolone (**14**) in 47% yield. The yield of petasitolone (**14**) was found to be improved by the use of Jone's oxidation. Thus, reaction of **128** with Jones reagent at 0°C for 10 min led to a complete disappearance of the starting material. Purification of the crude product by flash chromatography gave petasitolone (**14**) in 79% yield.

The synthetic petasitolone (**14**) showed spectra data (^{1}Hmr , ^{13}Cmr and ir) which were in agreement with those of natural petasitolone. (For a direct comparison of these spectral data see Figures 1 and 2.)



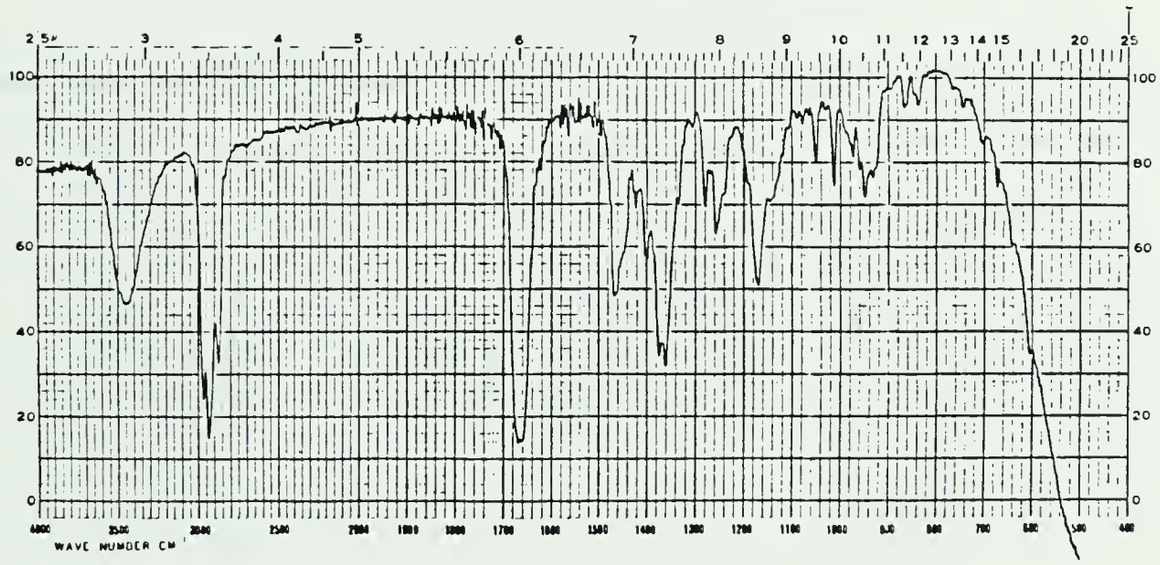


Figure 1. ^{1}Hmr and ir spectrum of natural petasitolone. ^{1}Hmr spectrum was recorded on a JEOL FX90Q spectrometer and ir spectrum was recorded on a HITACHI EPI-G3 spectrometer.

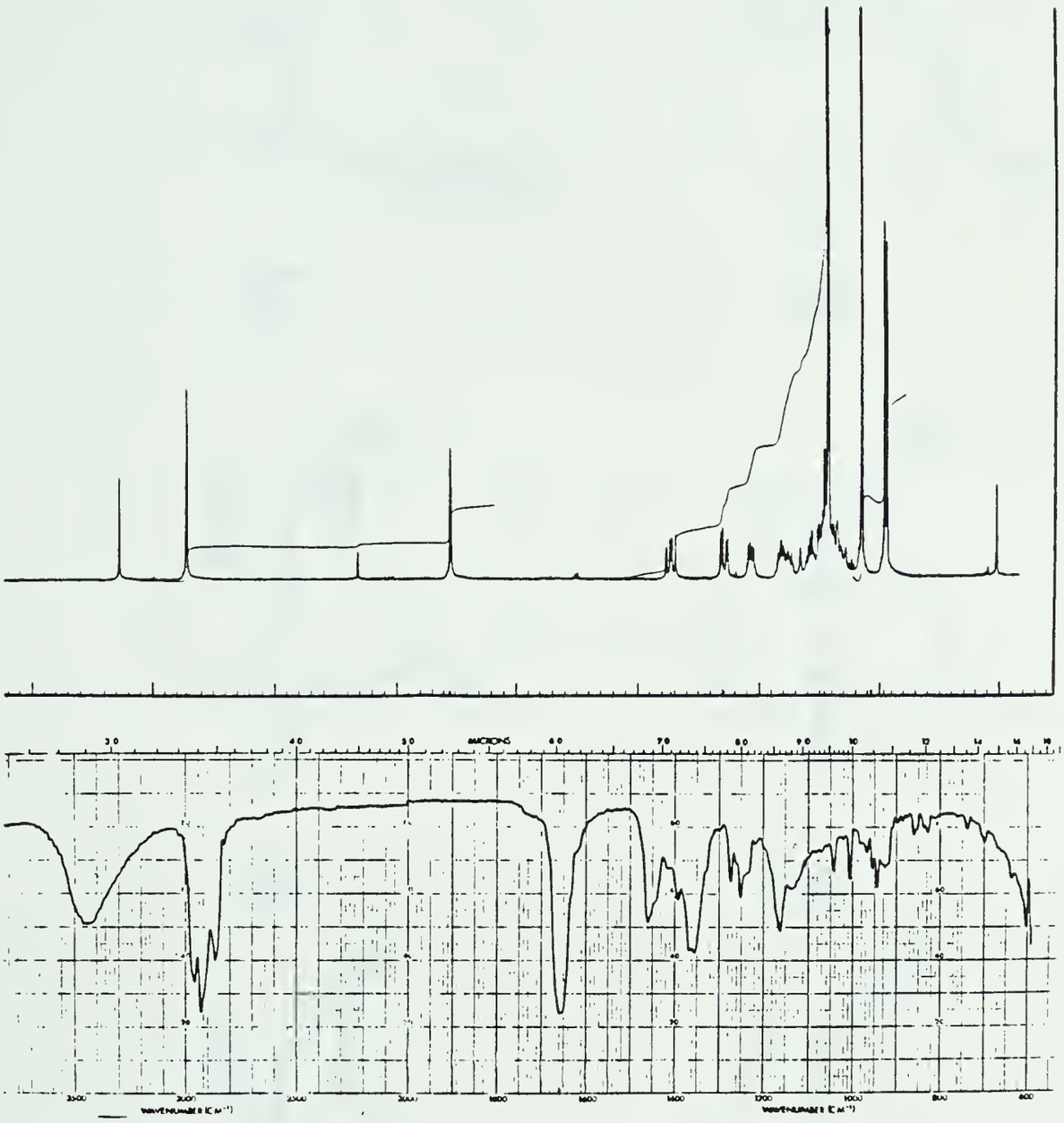
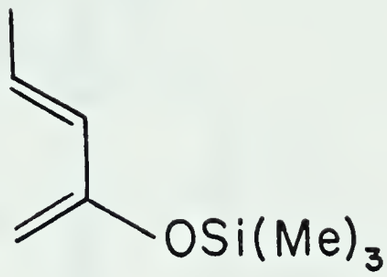


Figure 2. ^{1}Hmr and ir spectrum of synthetic petasitolone (**14**). ^{1}Hmr spectrum was recorded on a Bruker WH-400 and ir spectrum was recorded on a Perkin-Elmer model 457 spectrometer.



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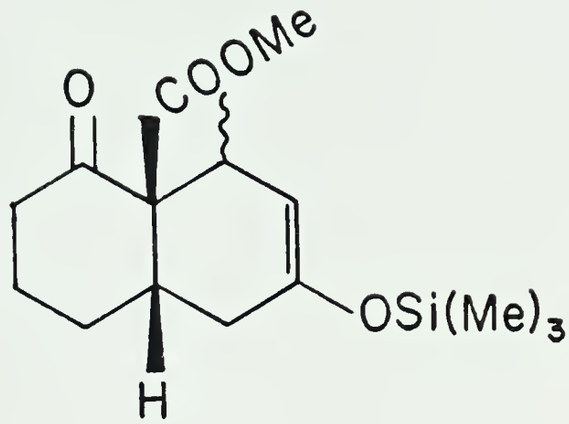

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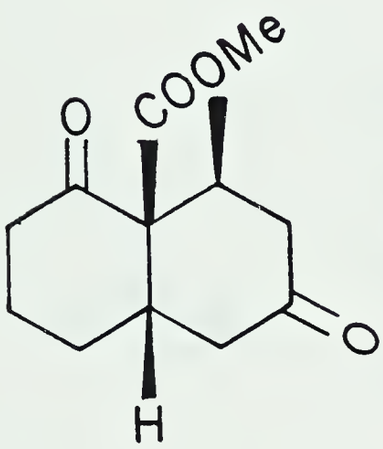

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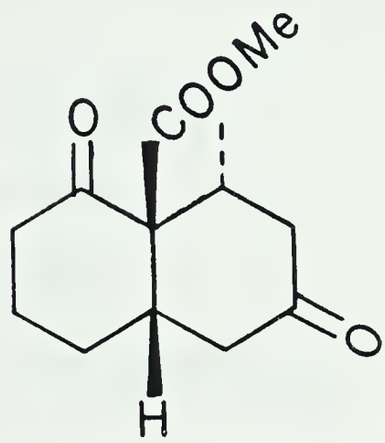

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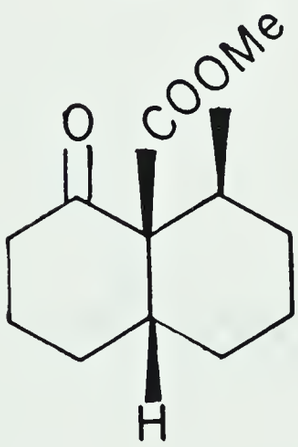

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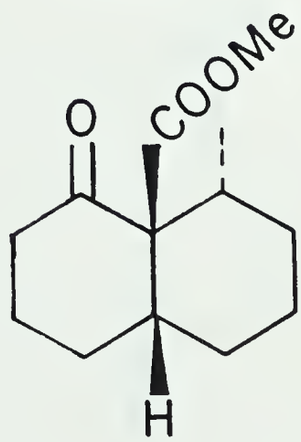

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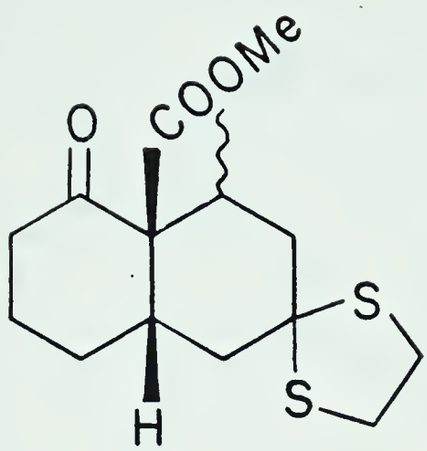

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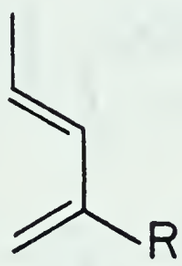

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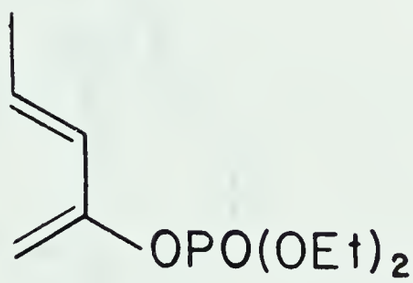
105 R = SPh

106 R = OAc

107 R = $OCOC(CH_3)_3$



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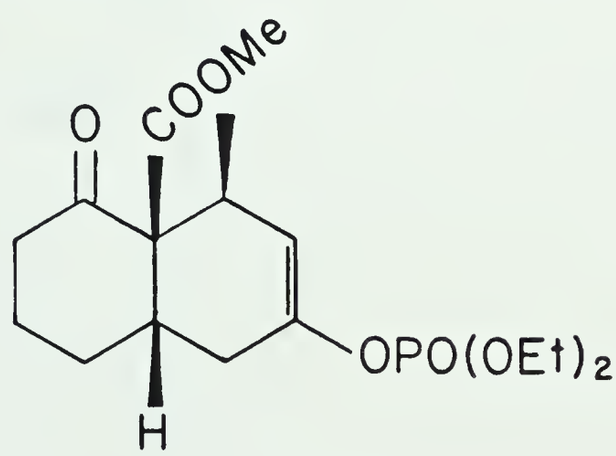

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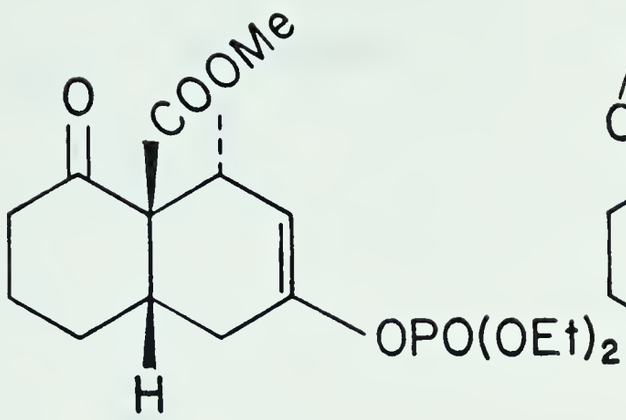

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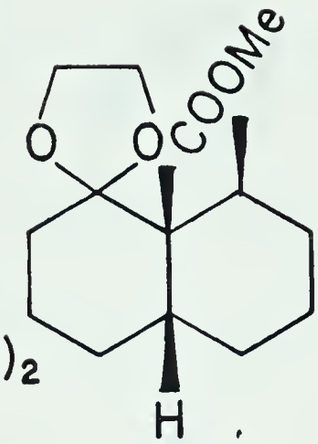

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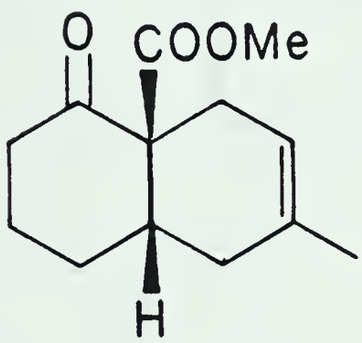

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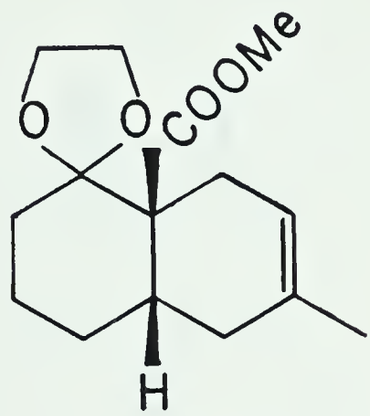

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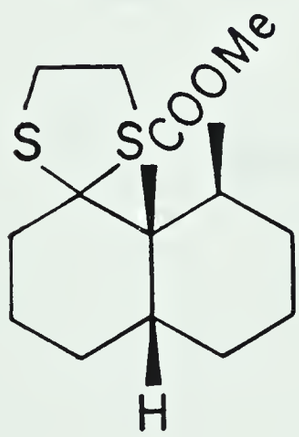

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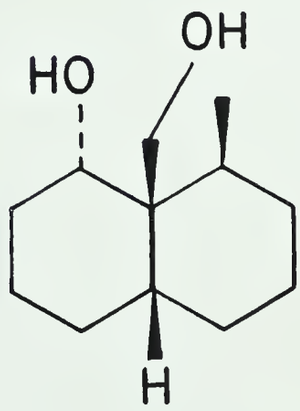

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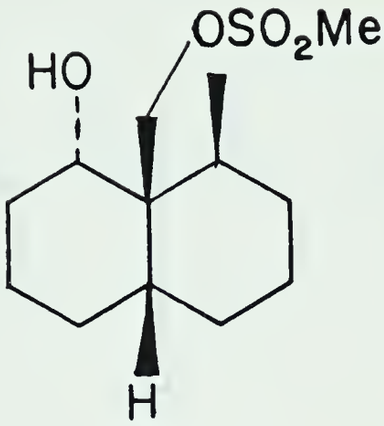

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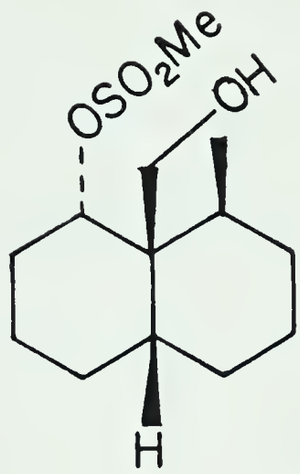

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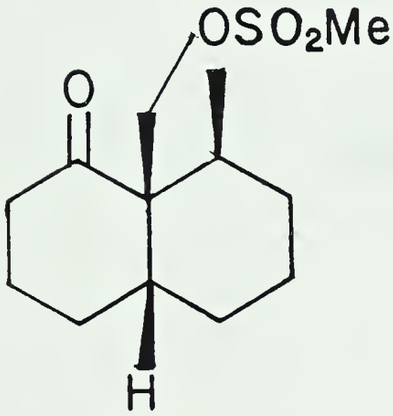

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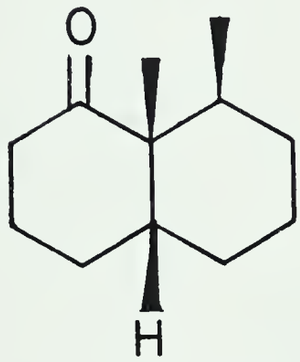

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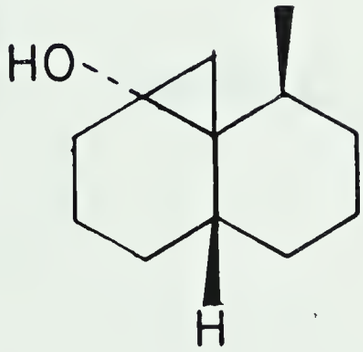

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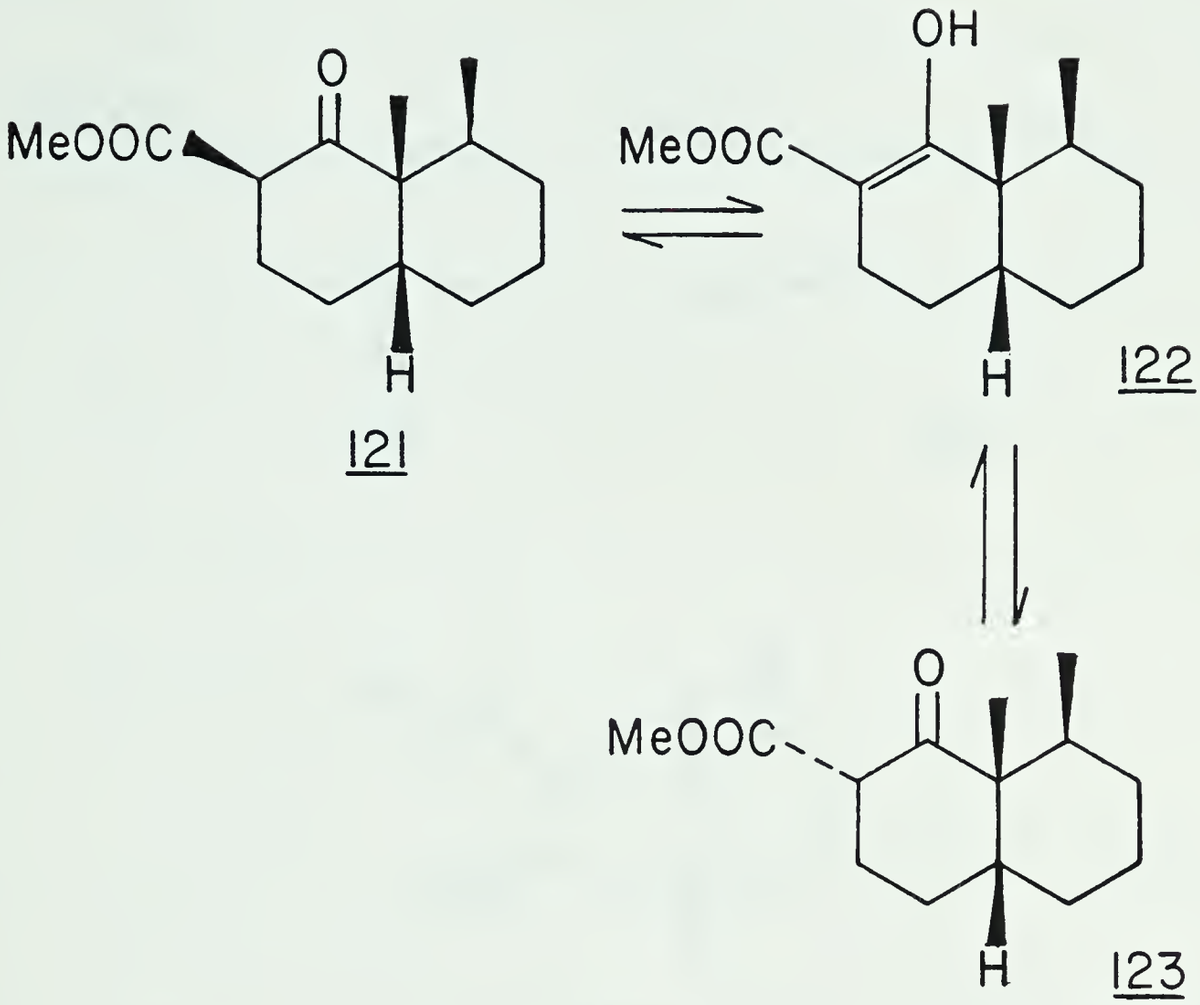
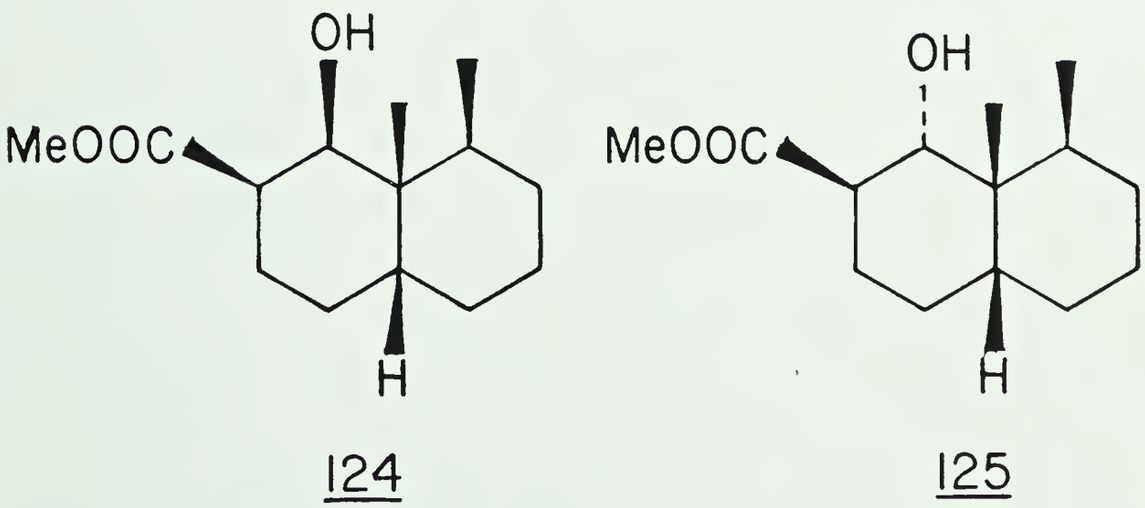
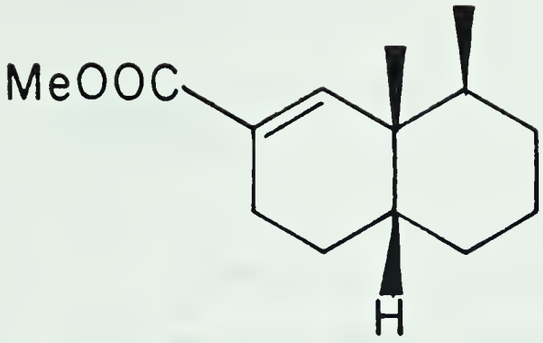
Scheme V


O
MeOOC
H
121
OH
MeOOC
H
122
O
MeOOC
H
123


OH
MeOOC
H
124
OH
MeOOC
H
125



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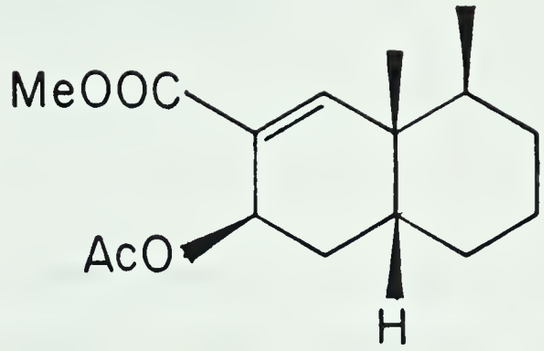

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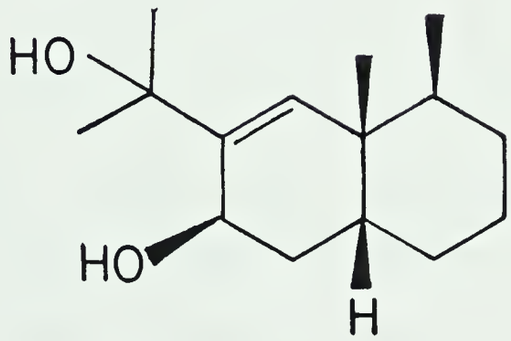

128

Experimental

General

Chemical ionization mass spectra (cims) were recorded on an AEI-MS12 spectrometer using ammonia gas as the ionizing medium. For other general remarks, see Chapter 1 of this thesis.

Materials

Benzene, ether and tetrahydrofuran were freshly distilled over lithium aluminum hydride. Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. Acetone was distilled over potassium permanganate crystals. Methylene chloride was washed with an equal volume of 10% aqueous sodium carbonate and distilled over powdered calcium chloride. Diisopropylamine was distilled over calcium hydride. N,N-dimethylformamide was distilled over phosphorus pentoxide. Methanol and ethanol were distilled over magnesium metal and stored over 3 Å molecular sieve. Nitrogen or argon was passed over a purification train of Fieser's solution,[79] saturated aqueous lead acetate, concentrated sulfuric acid and potassium hydroxide pellets. Enone-ester **89**[80,81] was prepared from

2-carbomethoxycyclohexanone according to the procedure described in Chapter 1 of this thesis. For the preparations of the 3:1 mixture of **99** and **100** and the 6:1 mixture of **109** and **110**, as well as the preparations of the keto-esters **101** and **102** from the 5:3 mixture of **90** and **91**, and from the 6:1 mixture of **109** and **110**, see Chapter 1 of this thesis.

8aβ-Carbomethoxy-8β-methyl-2,3,4,4aβ,5,7,8,8a-octahydro-1,6-naphthalenedione (**99**) and 8aβ-Carbomethoxy-8α-methyl-2,3,4,4aβ,5,7,8,8a-Octahydro-1,6-naphthalenedione (**100**)*.

a) Using a 1:1 mixture of ether and methylene chloride as the solvent.

At -50°C, anhydrous stannic chloride (261 mg, 1.00 mmol) was added to a solution of enone-ester **89** (369 mg, 2.01 mmol) and trans-2-trimethylsilyloxy-1,3-pentadiene (**97**) (936 mg, 6.00 mmol) in a 1:1 mixture of ether and methylene chloride (5 mL). Additional amount of **97** (624 mg, 4.00 mmol) in a 1:1 mixture of ether and methylene chloride (5 mL) was added. After stirring under an atmosphere of argon for 6 h the reaction mixture was warmed to room temperature and water was added. The resulting mixture was extracted

*The stereochemical designations used in this and all other chemical names used in this section denote relative stereochemistry. All compounds used and obtained were racemic.

with methylene chloride. The organic extracts were dried, filtered and conccentrated. Column chromatography of the residue on silica gel, eluting with 10-15% ethyl acetate in n-hexane gave an impure mixture of **99** and **101**. Another purification by flash chromatography on silica gel, eluting with 10% ethyl acetate in n-hexane gave a 7:1 mixture (by ^{1}Hmr integration) of the adducts **99** and **100** (218 mg; 46% yield) (for spectral data of **99** and **100**, see Chapter 1, Experimental section).

b) Using ether as the solvent at -50°C.

At -50°C, anhydrous stannic chloride (210 mg, 0.81 mmol) was added to a solution of enone-ester **89** (249 mg, 1.62 mmol) and trans-2-trimethylsilyoxy-1,3-pentdiene (**97**) (1.26 g, 8.08 mmol) in ether (10 mL). After stirring under an atmosphere of argon for 6 h the reaction mixture was warmed to room temperature and water was added. The resulting mixture was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10-15% ethyl acetate in n-hexane gave an impure mixture of adducts **99** and **100**. Another purification by flash chromatography on silica gel, eluting with 10% ethyl acetate in n-hexane gave a 7:1 mixture of pure adducts **99** and **100** (131 mg; 33% yield).

8aβ-Carbomethoxy-6,6-ethylenedithio-8-methyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (**103**).

At 0°C, 1,2-ethanedithiol (333 mg, 3.54 mmol) and boron trifluoride etherate (104 mg, 0.73 mmol) were sequentially added to a solution of a 7:1 mixture of diketones **99** and **100** (167 mg, 0.70 mmol) in methylene chloride (10 mL). After stirring under an atmosphere of argon for 30 min ice-cold 2.0 N aqueous sodium hydroxide was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in n-hexane gave a 7:1 mixture of thioketals **103** (198 mg; 90% yield) which showed the following spectral data: ir 1740 (ester C=O) and 1713 cm^{-1} (ketone C=O); ms M^+ 314.1008 (Calcd. for $C_{15}H_{22}O_3S_2$: 314.1010). The ^{1}Hmr spectrum of the mixture showed two sets of signals in an integral ratio of 7:1. The major set consisted of signals at δ3.74 (s, 3H, $-COOCH_3$) and 1.02 (d, 3H, J = 7.5 Hz, $-CH-C\underline{H}_3$). The minor set showed signals at δ3.80 (s, 3H, $-COOCH_3$) and 1.10 (d, 3H, J = 7.5 Hz, $-CH-C\underline{H}_3$).

8aβ-Carbomethoxy-8β-methyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (**101**) and 8aβ-Carbomethoxy-8α-octahydro-1(2H)-naphthalenone (**102**).

Raney nickel (*ca.* 2 g, grade W-2) was added to a solution of a 7:1 mixture of thioketals **103** (181 mg, 0.58 mmol) in ethanol (10 mL). The resulting mixture was heated to reflux for 2.5 h. Filtration and concentration gave a light yellow oil which was purified by column chromatography on silica gel. Elution with 1-2% ether in *n*-hexane gave the minor keto-ester **102** (11 mg; 8.6% yield) as a colorless oil. Continued elution gave the major keto-ester **101** (78 mg, 60% yield) (for spectral data of **101** and **102**, see Chapter 1, Experimental section).

8aβ-Carbomethoxy-1,1-ethylenedithio-8β-methyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**114**).

To a solution of keto-ester **101** (131 mg, 0.58 mmol) in 1,2-ethanedithiol (1.0 mL) at 0°C, was added boron trifluoride etherate (83 mg, 0.58 mmol). After stirring under an atmosphere of argon for 72 h an aqueous solution of 2.0 *N* sodium hydroxide was added. The resulting mixture was extracted with methylene chloride. The organic extracts were combined and washed with water, dried, filtered and

concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in n-hexane gave the pure thioketal **114** (84 mg; 48% yield): ^{1}Hmr δ3.68 (s, 3H, $-COOCH_3$), 3.15 (m, 4H, $-SCH_2CH_2S-$) and 1.31 (d, 3H, J = 6.5 Hz, $-CH-CH_3$); ir 1725 (ester C=O); ms M^+ 300.1216 (Calcd. for $C_{15}H_{24}O_2S_2$: 300.1219).

1α-Hydroxy-8aβ-hydroxymethyl-8β-methyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**115**).

At 0°C, a solution of sodium bis(2-methoxyethoxy) aluminium hydride (2.5 mL of 3.5 M, 8.75 mmol) in toluene was added to a solution of keto-ester **101** (340 mg, 1.53 mmol) in tetrahydrofuran (20 mL). After stirring under an atmosphere of nitrogen for 8 h the reaction mixture was cooled to 0°C and ice-water was added to destroy excess reducing agent. Ice-cold aqueous 2.0 N hydrochloric acid was added and the resulting mixture extracted with ether. The ethereal extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 50% ether in n-hexane gave pure diol **115** (289 mg; 96% yield). Recrystallization from a solution of ether and petroleum ether gave white needles of pure **115**: m.p. 97-99°C; ir 3317 cm^{-1} (-OH); ms m/e 180.1517 (M^+ - 18; Calcd. for $C_{12}H_{20}O$: 180.1515); ^{1}Hmr

δ4.35 (d, 1H, J = 12 Hz, -CH<u>H</u>-OH), 3.83 (dd, 1H, J = 14 Hz, J' = 6 Hz, -C<u>H</u>-OH), 3.71 (d, 1H, J = 12 Hz, -C<u>H</u>H-OH), 2.74, 2.26 (each broad s, each 1H, both -OH) and 1.17 (d, 3H, J = 7 Hz, -CH-C<u>H</u>$_3$). The two signals at δ2.74 and 2.26 disappeared on D_2O exchange. ^{13}Cmr δ79, 66, 44, 38, 32, 30, 29, 27, 26, 25, 21 and 19.

<u>Anal</u>. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.58; H, 11.06.

<u>1α-Hydroxy-8aβ-methanesulfonyloxymethyl-8β-methyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**116**)</u>.

Diol **115** (215 mg, 1.08 mmol) was dissolved in methylene chloride (10 mL) and cooled to -20°C. Pyridine (1.0 mL) and methanesulfonyl chloride (120 mg, 1.08 mmol) were sequentially added. After stirring under an atmosphere of argon for 28 h the reaction mixture was warmed to 0°C. A solution of 2.0 <u>N</u> aqueous hydrochloric acid was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 50% ether in <u>n</u>-hexane gave the mesylate **116** (274 mg; ~81% yield, based on consumed starting material) which was contaminated with a small amount (~10%) of **117**. Continued elution gave the diol **115**

(11 mg, 5% recovery). The following spectral data were recorded for **116**: ^{1}Hmr δ4.73 (d, 1H, J = 10 Hz, -CH<u>H</u>-OMS), 4.48 (d, 1H, J = 10 Hz, -C<u>H</u>H-OMS), 3.68 (m, 1H, -C<u>H</u>-OH), 3.08 (s, 3H, $-OSO_2CH_3$), 1.01 (d, 3H, J = 7.0 Hz, -CH-C<u>H</u>$_3$); ir 3550 (-OH), 2357 (s=O) and 1173 cm^{-1} (S=O); ms m/e: 180.1514 (M^+ - 96; Calcd. for $C_{12}H_{20}O$: 180.1515) and ms m/e 162.1408 (M^+ - 114; Calcd. for $C_{12}H_{18}$: 162.1409).

<u>8aβ-methanesulfonyloxymethyl-8β-methyl-3,4,4aβ,5,6,7,8,8a-1(2H)-naphthalenone (**118**)</u>.

Alcohol-mesylate **116** (260 mg, 0.94 mmol) was dissolved in acetone (8 mL) and cooled to 0°C. Jone's reagent (2.0 mL of 8.0 <u>N</u>, 16 mmol) was added. After stirring for 30 min water was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 30% ether in <u>n</u>-hexane gave pure keto-mesylate **118** (199 mg, 77% yield): ^{1}Hmr δ4.70 (d, 1H, J = 9.0 Hz, -C<u>H</u>H-OMS), 433 (d, 1H, J = 9.0 Hz, -CH<u>H</u>-OMS), 3.10 (s, 3H, $-OSO_2CH_3$) and 0.68 (d, 3H, J = 7.0 Hz, -CH-C<u>H</u>$_3$); ir (neat) 1703 (C=O), 1356 (S=O) and 1175 cm^{-1} (S=O); ms M^+ 274.1233 (Calcd. for $C_{13}H_{22}O_4S$: 274.1233).

8β 8aβ-Dimethyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (**119**) and 1α-hydroxy-1-8aβ-methano-8β-methyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**120**).

Keto-mesylate **118** (170 mg, 0.62 mmol), anhydrous sodium iodide (930 mg, 6.20 mmol) and zinc dust (811 mg, 12.4 mmol) were placed in N,N-dimethylformamide (10 mL). The resulting mixture was heated to reflux for 52 h. After cooling to room temperature, the reaction mixture was filtered. The organic filtrate was washed with ice-cold 2.0 N aqueous hydrochloric acid, water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in n-hexane gave pure ketone **119** (67 mg; 60% yield). Further elution with 5% ether in n-hexane gave the cyclopropanol **120** (23 mg; 21% yield). The ketone **119** has the following spectral data: ^{1}Hmr δ1.08 (s, 3H, -C-CH_3) and 0.67 (d, 3H, J = 7.0 Hz, -CH-CH_3); ^{13}Cmr δ216.0, 51.0, 45.0, 38.0, 31.7, 30.0, 26.8, 26.4, 21.0, 16.0 and 14.6; ir 1706 cm^{-1} (C=O); ms M^+ 180.1515 (Calcd. for $C_{12}H_{20}O$: 180.1509). The following spectral data were recorded for the cyclopropanol **120**: ^{1}Hmr δ1.07 (d, 3H, J = 7.0 Hz, -CH-CH_3), 0.69 (d, 1H, J = 5.5 Hz, cyclopropyl H) and 0.25 (dd, 1H, J = 5.5 Hz, J' = 1.5 Hz, cyclopropyl H); ir 3443 cm^{-1} (-OH); ms M^+ 180.1521 (Calcd. for $C_{12}H_{20}O$: 180.1509).

Conversion of Cyclopropanol **120** to Ketone **119**.

Cyclopropanol **120** (21 mg, 0.12 mmol) and sodium hydroxide (25 mg, 0.63 mmol) were added to a solution of water and N,N-dimethylformamide (1:2; 2 mL) and heated to reflux. After 8 h the reaction mixture was cooled to room temperature and diluted with n-hexane. An aqueous solution of saturated ammonium chloride was added and the resulting mixture separated. The aqueous phase was extracted with n-hexane. The organic extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in n-hexane gave the ketone **119** (10 mg; 48% yield).

2-Carbomethoxy-8β,8aβ-dimethyl-3,4,4aβ,5,6,7,8,8a-octahydro-1(2H)-naphthalenones (**121**), (**122**) and (**123**).

Sodium hydride (60% dispersion in oil, 0.57 g, 14.3 mmol) and dimethyl carbonate (4.3 g, 47.8 mmol) were added to benzene (50 mL) and heated to reflux. A solution of ketone **119** (733 mg, 4.07 mmol) in benzene (20 mL) was added dropwise over 20 min. After refluxing for 50 h, the reaction mixture was cooled to 0°C and methanol was added with vigorous stirring to destroy excess sodium hydride. An ice-cold aqueous solution of 10% acetic acid was added. The

resulting mixture was extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether gave the mixture of keto-enol tautomers **121**, **122** and **123** (890 mg; 88% yield). The ^{1}Hmr spectrum showed three sets of signals corresponding to the three compounds in the mixture of keto-enol tautomers. Signals appeared at δ12.72 (s, ~0.5H enolic H), 3.74, 3.73, 3.70 (each s, total 3H, $-COOCH_3$), 1.15, 1.11, 1.05 (each s, total 3H, $-C-C\underline{H}_3$) and 0.95, 0.73, 0.66 (each d, total 3H, $-CH-C\underline{H}_3$); ir 1748, 1702, 1640 and 1604 cm^{-1} (β-keto ester); ms M^+ 238.1572 (Calcd. for $C_{14}H_{22}O_3$: 238.1563).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.27; H, 9.31.

2β-Carbomethoxy-1β-hydroxy-8β,8aβ-dimethyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**124**) and 2β-Carbomethoxy-1α-hydroxy-8β-8aβ-dimethyl-1,2,3,4,4aβ,5,6,7,8,8a-perhydronaphthalene (**125**).

A mixture of keto-enol tautomers **121**, **122** and **123** (65 mg, 0.27 mmol) was dissolved in methanol (2 mL) and cooled to 0°C. Sodium borohydride (33 mg, 0.87 mmol) was added. After stirring for 30 min water was added, followed by an

aqueous solution of saturated ammonium chloride. The resulting mixture was extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ether in petroleum ether gave a single diastereomeric alcohol **124** (13 mg, 20% yield) as a colorless oil: ir 3480 (-OH) and 1728 cm^{-1} (C=O); ms M^+ 240.1720 (Calcd. for $C_{14}H_{24}O_3$: 240.1726); ^{1}Hmr δ3.76 (s, 3H, $-COOCH_3$), 3.62 (dd, 1H, J = 6.0 Hz, J' = 5.0 Hz, -C<u>H</u>-OH), 3.35 (d, 1H, J = 6.0 Hz, -CH-O<u>H</u>), 2.83 (ddm, 1H, J = 10 Hz, J' = 5.0 Hz, $-CH-COOCH_3$), 1.00 (s, 3H, $-C-CH_3$) and 0.91 (d, 3H, J = 7.0 Hz, -CH-C<u>H</u>$_3$). After D_2O exchange the signal at δ3,35 disappeared and the dd at δ3.62 collapsed to a doublet with coupling constant of 5.0 Hz. Continued elution gave another isomeric alcohol **125** (45 mg, 69% yield) which was recrystallized from ether/petroleum ether to give pure white crystals of **125**, m.p. 82-84°C; ir 3510 (-OH) and 1719 cm^{-1} (C=O); ms M^+ 240.1723 (Calcd. for $C_{14}H_{24}O_3$: 240.1726); ^{1}Hmr δ3.74 (s, 3H, $-COOCH_3$), 3.53 (dd, 1H, J = 11 Hz, J' = 4.5 Hz, -C<u>H</u>-OH), 2.73 (ddd, 1H, J = 13 Hz, J' = 11 Hz, J" = 4.0 Hz, -C<u>H</u>P$COOCH_3$), 2.46 (d, 1H, J = 4.5 Hz, -CH-O<u>H</u>), 1.12 (s, 3H, -C-C<u>H</u>$_3$). After D_2O exchange, the doublet at δ2.46 disappeared and the signal at δ3.53 changed to a doublet (J = 11 Hz).

Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.66. Found: C, 70.10; H, 10.15.

2-Carbomethoxy-8β-8aβ-dimethyl-3,4,4aβ5,6,7,8,8a-octahydronaphthalene (**126**).

A mixture of alcohols **124** and **125** (217 mg, 0.90 mmol), dicyclohexylcarbodiimide (279 mg, 1.36 mmol) and copper(I) chloride (43 mg) were added to N,N-dimethylformamide (5 mL) and heated to reflux. After 10 h the reaction mixture was cooled to room temperature and diluted with methylene chloride (10 mL). A solution of 10% aqueous acetic acid was added. After stirring for 1.5 h the reaction mixture was diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ether in petroleum ehter gave the pure unsaturated ester **126** (150 mg; 75% yield) as a colorless oil: ^{1}Hmr δ6.90 (dd, 1H, J = 2.0 Hz, J' = 1.5 Hz, -C=CH-), 3.76 (s, 3H, $-COOCH_3$), 2.43 (dddd, 1H, J = 17 Hz, J' = 6.0 Hz, J" = 3.0 Hz, J'" = 1.5 Hz, =C-CH<u>H</u>-, equatorial), 2.19 (dddd, 1H, J = 17 Hz, J' = 10 Hz, J" = 6.0 Hz, J"' = 2.00 Hz, =C-CH<u>H</u>-, axial), 1.04 (s, 3H, $-C-CH_3$) and 0.91 (d, 3H, J = 7.0 Hz, $-CH-C\underline{H}_3$); ir 1717 (C=O) and 1642 cm^{-1} (C=C); ms M^+ 222.1618 (Calcd. for $C_{14}H_{22}O_2$: 222.1625).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.75; H, 10.06.

2-Carbomethoxy-8β,8aβ-dimethyl-3,4,4aβ 5,6,7,8,8a-octahydronaphthalene (**126**).

Alcohol **125** (58 mg, 0.24 mmol), dicyclohexylcarbodiimide (77 mg, 0.36 mmol) and copper(I) chloride were placed in N,N-dimethylformamide (5 mL) and heated to reflux. After 48 h the reaction mixture was cooled to room temperature and a solution of 10% aqueous acetic acid (10 mL) was added. After stirring for 6 h the reaction mixture was diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether gave the pure unsaturated ester **126** (45 mg; 84% yield) as a colorless oil.

3β-Acetoxy-2-carbomethoxy-8β-8aβ-dimethyl-3,4,4aβ 5,6,7,8,8a-octahydronaphthalene (**127**).

Unsaturated ester **126** (105 mg, 0.47 mmol) and selenium dioxide (63 mg, 0.57 mmol) were added to glacial acetic acid (4 mL) and the resulting mixture heated to reflux. After 24 h an additional batch of selenium dioxide (63 mg, 0.57 mmol) and glacial acetic acid (2 mL) was added. After another 25

h the reaction mixture was cooled to room temperature and potassium acetate (200 mg) was added. The reaction mixture was filtered and the residue washed thoroughly with methylene chloride. The organic filtrate was washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 10% ether in petroleum ether gave the allylic acetate **127** (81 mg; 61% yield). A single recrystallization from a solution of ether in petroleum ether gave pure white crystals of **127**, m.p. 119-120°C: ^{1}Hmr δ7.22 (s, 1H, -C=CH-), 5.74 (dd, 1H, J = 40 Hz, J' = 1.5 Hz, -CH-OAc), 3.75 (s, 3H, $-COOCH_3$), 2.03 (s, 3H, -OAc), 1.10 (s, 3H, $-C-CH_3$) and 0.89 (d, 3H, J = 7.0 Hz, $-CH-\underline{CH_3}$); ir 1737 (acetate C=O) and 1723 cm^{-1} (carbomethoxyl C=O); ms M^+ 280.1650 (Calcd. for $C_{16}H_{24}O_4$: 280.1675).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.54; H, 8.59.

3β-Hydroxy-2(2-hydroxyisopropyl)-8β,8aβ-dimethyl-3,4,4aβ,5,6,7,8,8a-octahydronaphthalene (**128**).

Diester **127** (57 mg, 0.20 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to -78°C. Methyllithium (0.77 mL of 1.6 M, 1.22 mmol) was added. The reaction mixture was allowed to warm up to room temperature. Ice-

cold water was added to destroy excess methyllithium. The resulting mixture was extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Purification of the residue by flash chromatography, eluting with 25% ethyl acetate in petroleum ether gave the diol **128** (45 mg; 93% yield): ^{1}Hmr δ5.74 (s, 1H, -C=CH-), 4.51 (dd, 1H, J = 4.5 Hz, J' = 2.0 Hz, -C<u>H</u>-OH), 1.47 (s, 3H, -C(OH)-C<u>H</u>$_3$), 1.39 (s, 3H, -C(OH)-C<u>H</u>$_3$), 1.00 (s, 3H, -C-CH$_3$) and 0.84 (d, 3H, J = 7.0 Hz, -CH-C<u>H</u>$_3$); ir 3480 and 3377 cm^{-1} (both -OH); cims M$^+$ 238 ($C_{15}H_{26}O_2$).

<u>Petasitolone (**14**)</u>.

a) <u>Oxidation of **128** with Pyridinium Dichromate</u>.

Diol **128** (12.8 mg, 0.05 mmol) and pyridinium dichromate (24 mg, 0.07 mmol) were added to methylene chloride (2 mL). After stirring under an atmosphere of nitrogen for 40 min the reaction mixture was filtered and the residue washed thoroughly with methylene chloride. The organic filtrate was concentrated and the residue purified by flash chromatography. Elution with 20% ethyl acetate in petroleum ether gave petasitolone (**14**) (6 mg; 47% yield): ^{1}Hmr δ6.73 (s, 1H, -C=CH-), 4.55 (s, 1H, -OH, disappeared on deuterium exchange with D_2O), 2.73 (dd, 1H, J = 16 Hz, J' = 12 Hz, -CHH-C=O, axial), 1.46 (s, 6H, 2 x CH$_3$), 1.07 (s, 3H,

-C-CH_3) and 0.97 (d, 3H, J = 7.0 Hz, -CH-$\underline{CH_3}$); ^{13}Cmr 202.6, 154.7, 141.3, 71.7, 40.7, 39.4, 38.6, 35.8, 30.2, 29.3, 29.1, 26.9, 20.7, 20.4 and 15.8; ir 3450 (-OH) and 1719 cm^{-1} (C=O); ms M^+ 236.2141 (Calcd. for $C_{15}H_{24}O_2$: 236.2142).

b) Oxidation of **128** with Jone's Reagent.

Diol **128** (12.9 mg, 0.05 mmol) was dissolved in acetone (2 mL) and cooled to 0°C. Jone's reagent (0.5 mL of 8 N, 4.0 mmol) was added. After stirring for 10 min water was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether gave pure petasitolone (**14**) (10.1 mg, 79% yield).

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CHAPTER 3

Synthetic Studies on Strophanthidin and Related Compounds

Introduction

Steroids of both natural and unnatural origins are well known to exhibit a wide spectrum of biological activities.[1] Among them are the cardiac-active steroidal glycosides which are of immense value in the treatment of heart diseases.[2,3] Some of these are known to improve cardiac efficiency, increase the contractibility of the heart muscle and diminish the heart rate.

Strophanthidin (**1**) is one of the more elaborate and complex aglycone of these cardiac-active glycosides. It is obtained from the glycosides present in the seeds of *Strophanthus kombe* by a series of enzymatic and acid hydrolysis.[1] The sugar residue of the glycoside is usually linked by a glycosidic bond to the C-3 hydroxyl of strophanthidin (**1**). The structural elucidation of strophanthidin was achieved after extensive chemical degradation studies[1] which finally led to the assignment of structure **1** for strophanthidin. Prominent in the structure of strophanthidin (**1**) is the β-orientated butenolide ring at C-17, as well as the *cis* stereochemistry for the A/B and C/D ring junctions. This latter characteristic is also present in most cardiac-active steroids. Other features of **1** include the presence of two tertiary hydroxyls at C-5 and C-14, as well as the angular aldehyde group at the C-10

position.

Very few synthetic studies have been reported for strophanthidin (**1**). Previous synthetic efforts have resulted in a partial synthesis[4] as well as the synthesis of 14-deoxy-14α-strophanthidin (**2**).[5,6] Other related work includes the synthesis of 14-deoxy-14α-strophanthidol (**3**).[7]

The partial synthesis of **1** which was reported by E. Yoshii and co-workers,[4] utilized the readily available pregnenolone acetate **4** as starting material. The first stage of the synthesis involved the introduction of an oxygen functionality to the unactivated C-19 position. This was achieved by treatment of pregnenolone acetate **4** with hypobromous acid, followed by reaction of the resulting bromohydrin derivative with lead tetraacetate to give the bromo-ether **5** which has the desired C-19 oxygen functionality. The latter compound was converted in four steps to the dienone **6** which was transformed to enone **7**.

The conversion of **6** to the enone **7** required the key task of introduction of the butenolide moiety at the C-17 position. It involved the initial transformation of **6** to the 21-methylthio derivative **8** using a base catalysed reaction with diethyl oxalate, followed by the reaction of the resulting 21-oxalyl derivative with methyl thiotosylate in the presence of excess potassium acetate in ethanol. Reaction of the diacetate derivative of **8** with methyl

bromoacetate and zinc dust in refluxing benzene gave the Reformatsky product **9**. Treatment of **9** with an equivalent of trimethyloxonium tetrafluoroborate gave the corresponding methyl sulfonium salt which was stirred in dichloromethane with dilute sodium hydroxide to give the β,δ-epoxy ester **10**. The latter compound was absorbed on a neutral alumina column and after several hours the column was eluted to furnish **11** which was transformed into **7** in another four steps.

The C-14 β-hydroxyl group was introduced as follows. Treatment of **7** with hypobromous acid gave an intermediate bromohydrin derivative which was then treated with Raney-nickel to give the alcohol **12**. Introduction of the other hydroxyl group to C-5 was early achieved by reaction with potassium bicarbonate which hydrolysed the acetate group at C-19, followed by alkaline hydrogen peroxide to give the epoxide **13**.

Final transformation to strophanthidin (**1**) proceeded <u>via</u> the selective oxidation of the angular hydroxymethyl moiety of the tetraol **14** with chromium trioxide in hexamethylphosphoric triamide.[4]

The synthesis of the 14-deoxy-14α-strophanthidin (**2**) and its related analog 14-deoxy-14α-strophanthidol (**3**) was reported by Kocovsky and co-workers.[5,6,7] The starting material used, was again pregnenolone acetate **4**. The

introduction of the C-19 oxygen functionality was similarly achieved by its conversion to the bromo-ether **5**.[8] However, they utilized an intramolecular Wittig reaction for the construction of the butenolide ring as follows. The bromo-ether **5** was converted to the 21-hydroxy derivative **15**. The 21-hydroxyl group **15** was introduced using lead tetraacetate in the presence of boron trifluoride etherate to give initially a derivative having a 21-acetoxy group which was then hydrolysed. Compound **15** was esterified with diethylphosphonoacetic acid in the presence of dicyclohexylcarbodiimide. The resulting ester **16** was cyclized without isolation with potassium t-butoxide to give the cardadienolide **17**. The latter compound was transformed to the unsaturated formate **18** which was treated with hypobromous acid to give the bromo-hydrin **19** whereby an oxygen functionality was introduced at the C-5 position with the required β-orientation. Finally, **19** was converted into 14-deoxy-14α-strophanthidin (**2**)[5,6] and 14-deoxy-14α-strophanthidol (**3**).[7]

A viable synthetic approach for the rapid assembly of the tetracyclic steroidal nucleus of strophanthidin (**1**) and related compounds would be to fuse the enone-ester **20** with the diene **21** by a Diels-Alder reaction to give adduct **22** which has most of the crucial features of the target molecule, except the ring D (Scheme I). This required five-

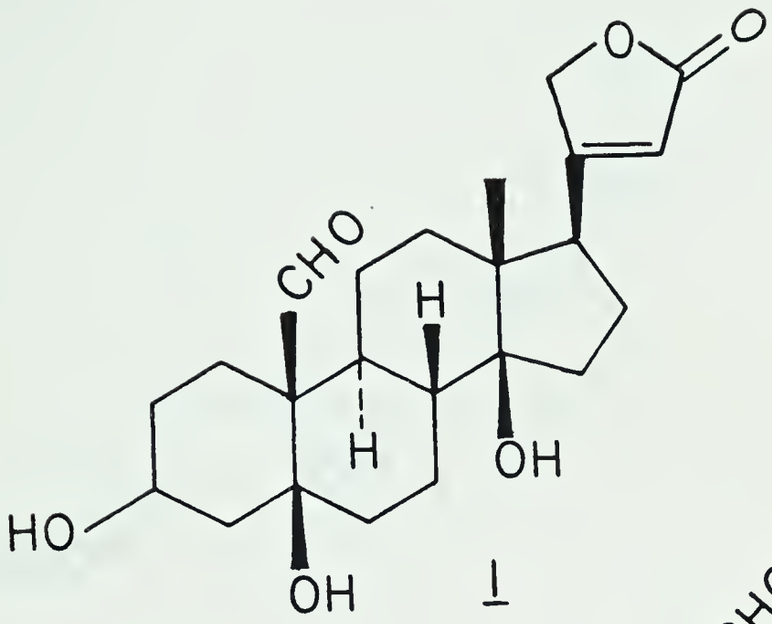
membered ring can be formed by a regioselective ring expansion of the cyclobutanone ring of the intermediate **23** to give **24**, using the known method developed by Liu and Ogino.[9] Compound **24** would have the tetracyclic skeleton of **1** and would only require further functional group modifications and introduction of the butenolide moiety to give strophanthidin (**1**). The synthetic strategy is outlined as shown in Scheme I.

An analysis of the Diels-Alder reaction of enone-ester **20** and the diene **21** indicated that there are four possible reaction pathways proceeding <u>via</u> the diastereomeric transition states **22a**, **25a**, **26a** and **27a**, to give the corresponding adducts **22**, **25**, **26** and **27**, respectively (Scheme II). Addition of diene **21** from the bottom face of the enone-ester **20** would proceed <u>via</u> transition states **22a** and **25a**, leading to the adducts **22** and **25** respectively. Addition from the top face of **20** would proceed <u>via</u> transition states **26a** and **27a** to give the adducts **26** and **27** respectively. Adduct **22**, resulting from addition <u>via</u> transition state **22a** is the required compound for the proposed synthesis of **1**.

In the study[10] of the Diels-Alder reactions of enone-ester **20**, it was observed that the adducts obtained, arose predominantly from the addition of the diene <u>endo</u> to the ester group of **20** (see Chapter 1). It would therefore be

expected that the Diels-Alder reaction as outlined in Scheme II would give predominantly the adducts **22** and **26**, resulting from additions of diene endo to the ester group of the dienophile. Futhermore, the bicyclo[4.2.0] octane ring system of the diene **21** would have a far more sterically hindered concave face and therefore, the addition of the dienophile should occur preferentially from the less hindered convex face of the diene **21**. If these expectations were to be borne out, then, the required adduct **22** could be formed predominantly.

The primary objective of this study is to explore the key Diels-Alder reaction of enone-ester **20** and the diene **21** with the objective of an efficient synthesis of the required intermediate **22**. The results of this study using the easily available dienes **28** and **29** for the Diels-Alder reaction will be described in this chapter of the thesis.



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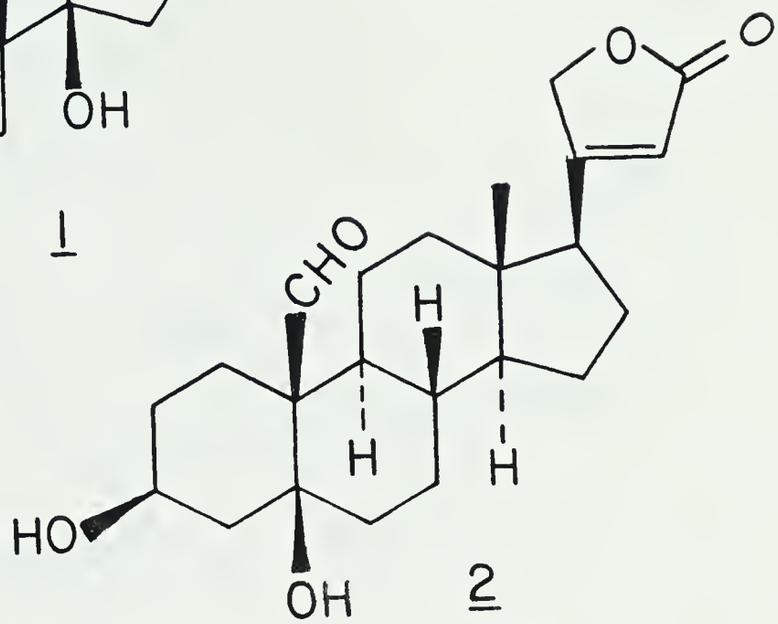

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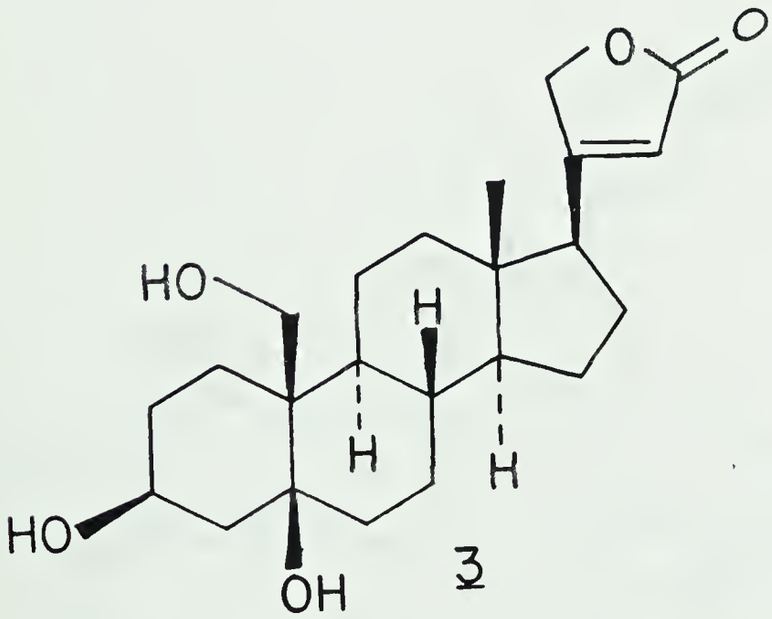

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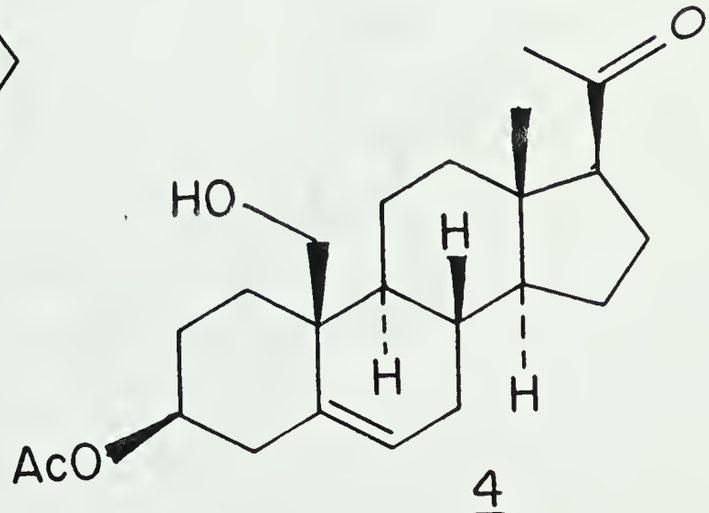

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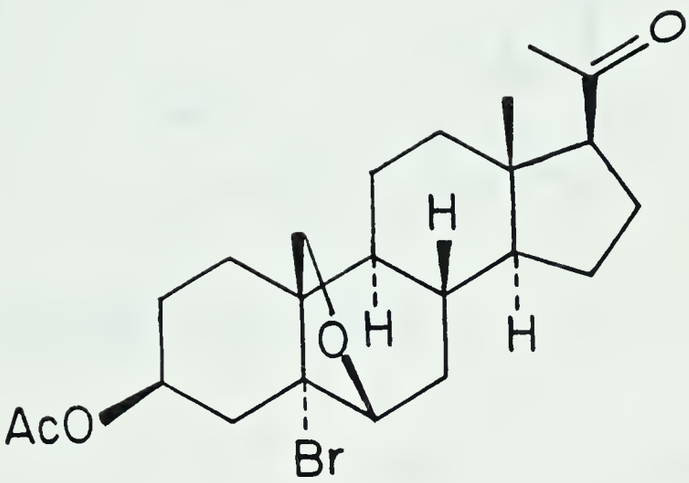

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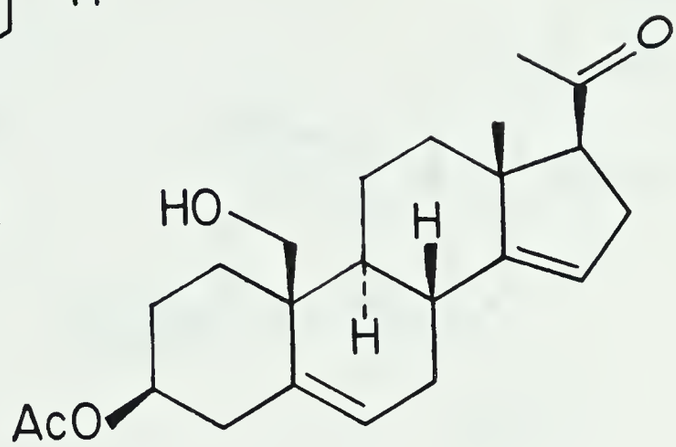

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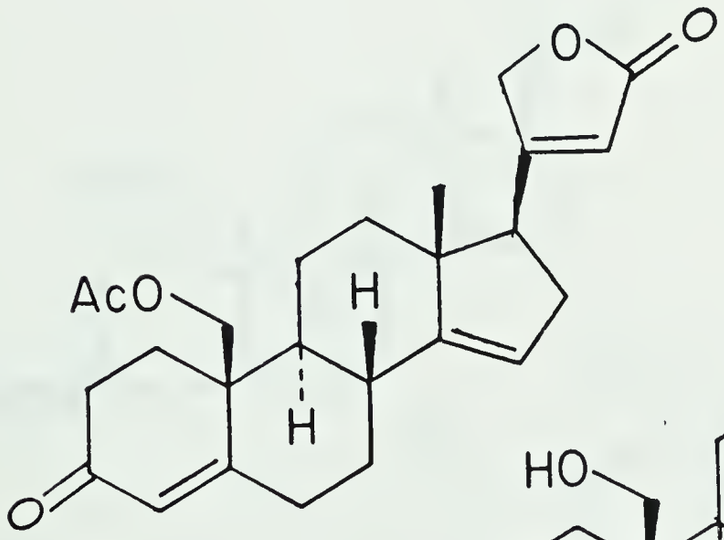

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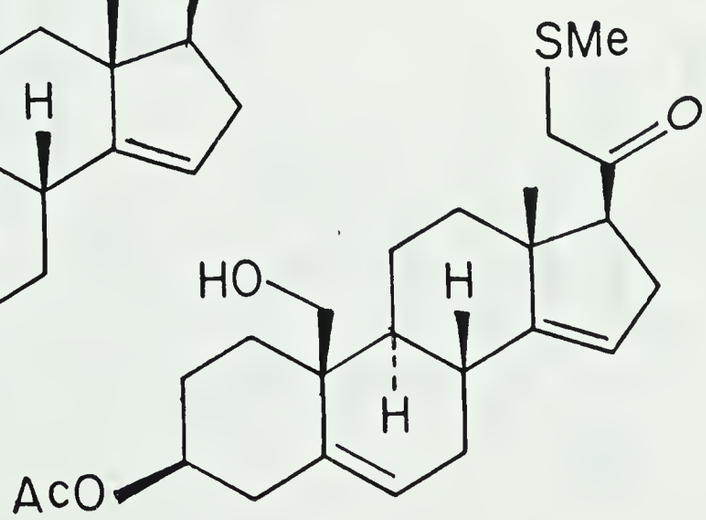

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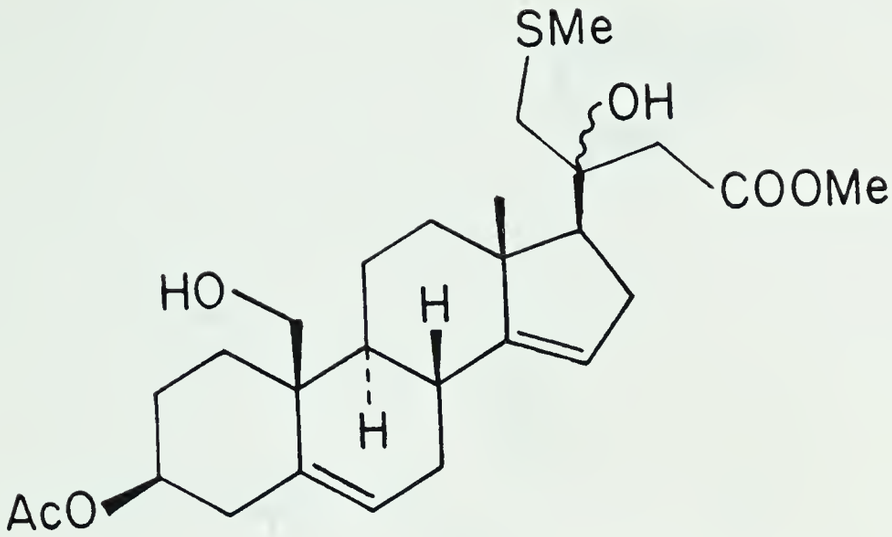
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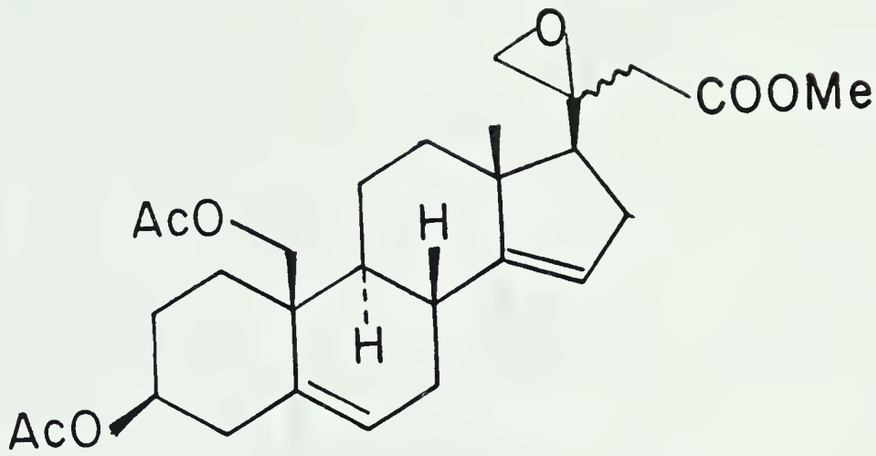
HO
H
H
AcO

9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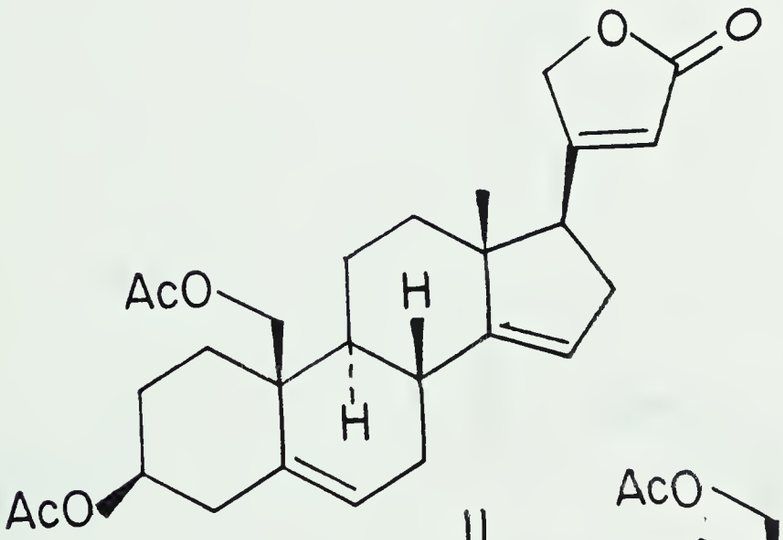
COOMe
AcO
H
H
AcO

10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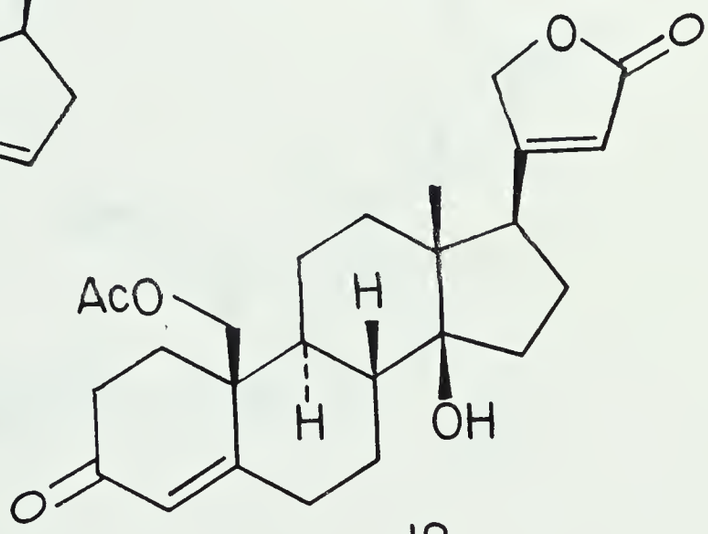
O
AcO
H
H
AcO

11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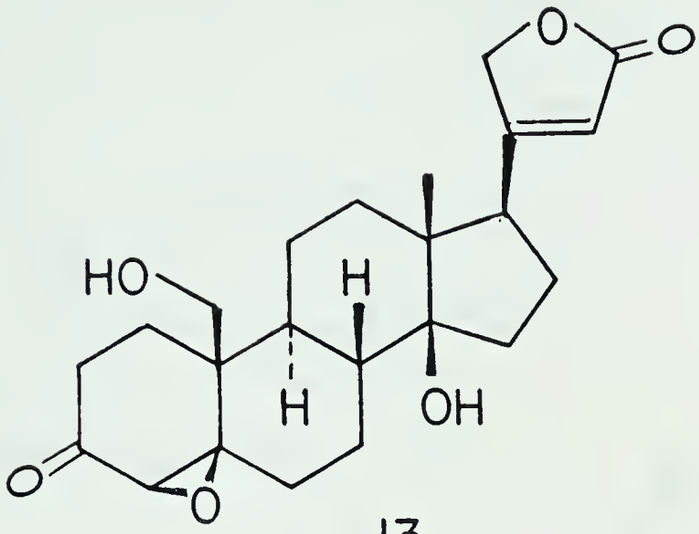
H
H
OH
O

12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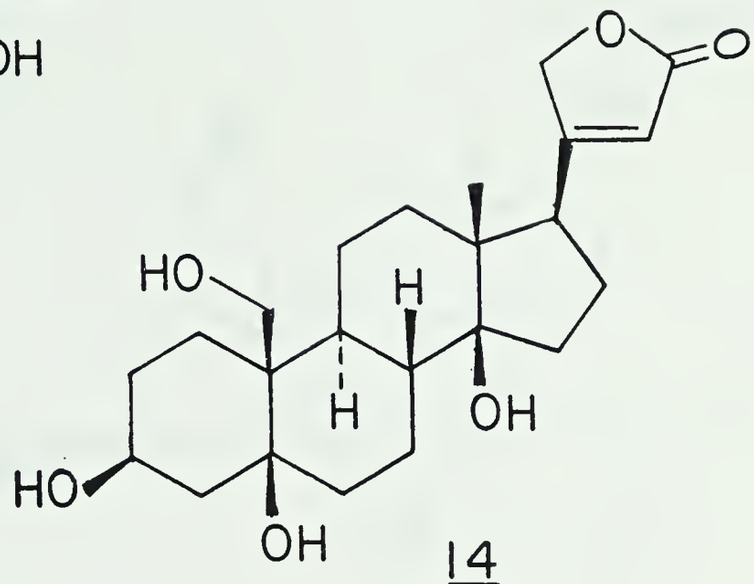
O
HO
H
H
OH
O
O

13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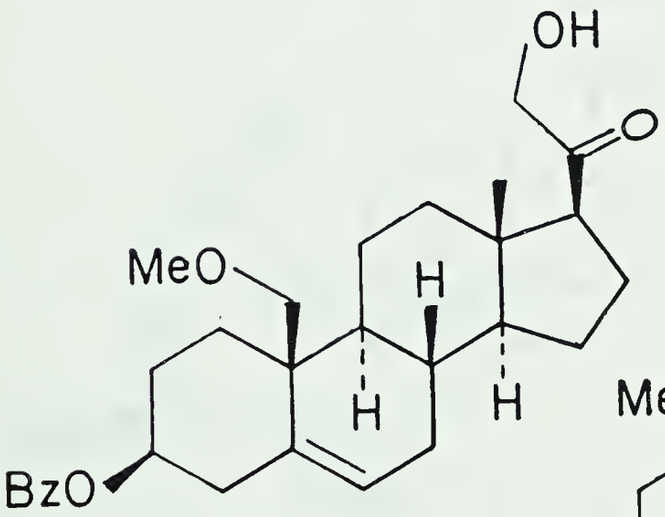
HO
H
H
OH
HO
OH

14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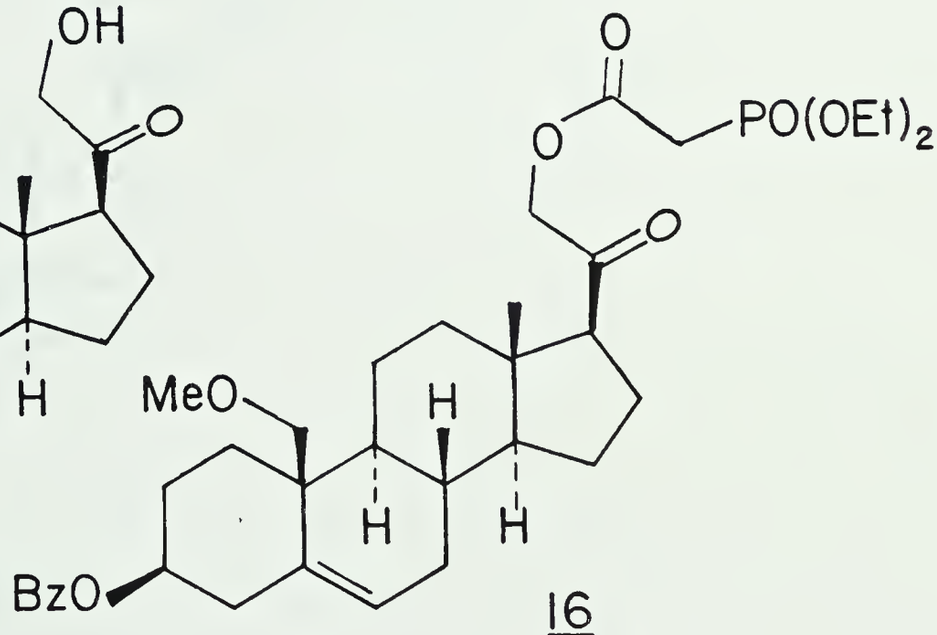
MeO
H
H
H
BzO

15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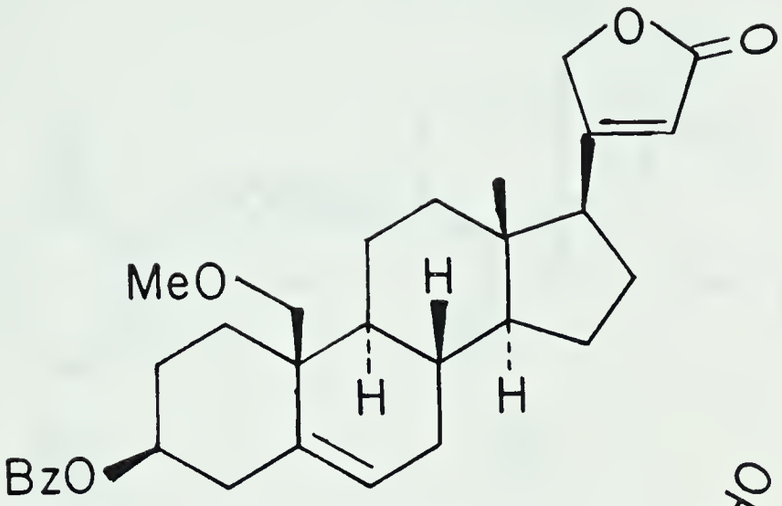
O
PO(OEt)2
O
MeO
H
H
H
BzO

16



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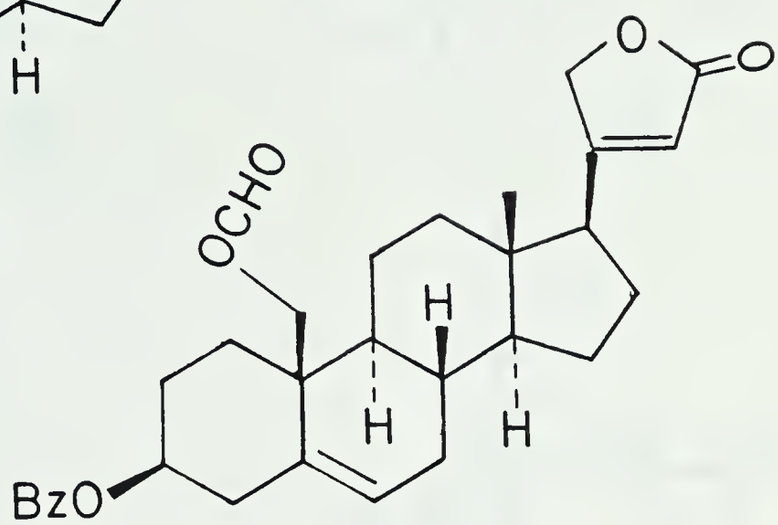

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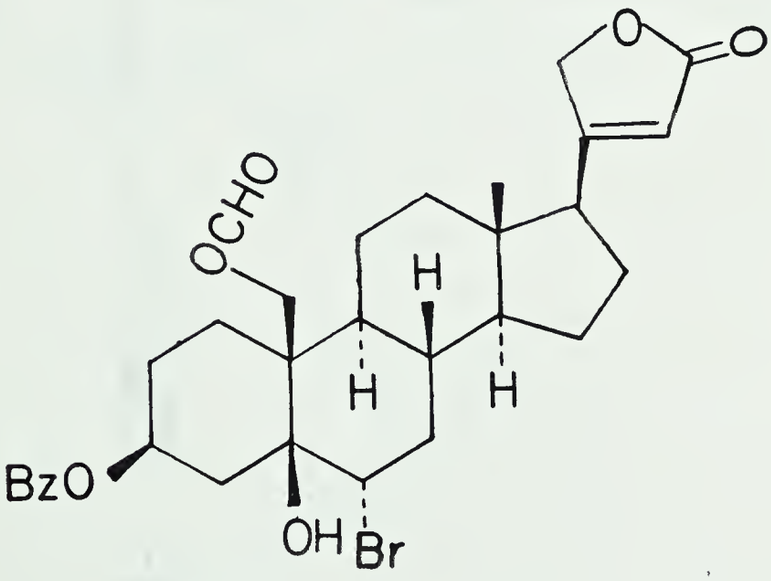
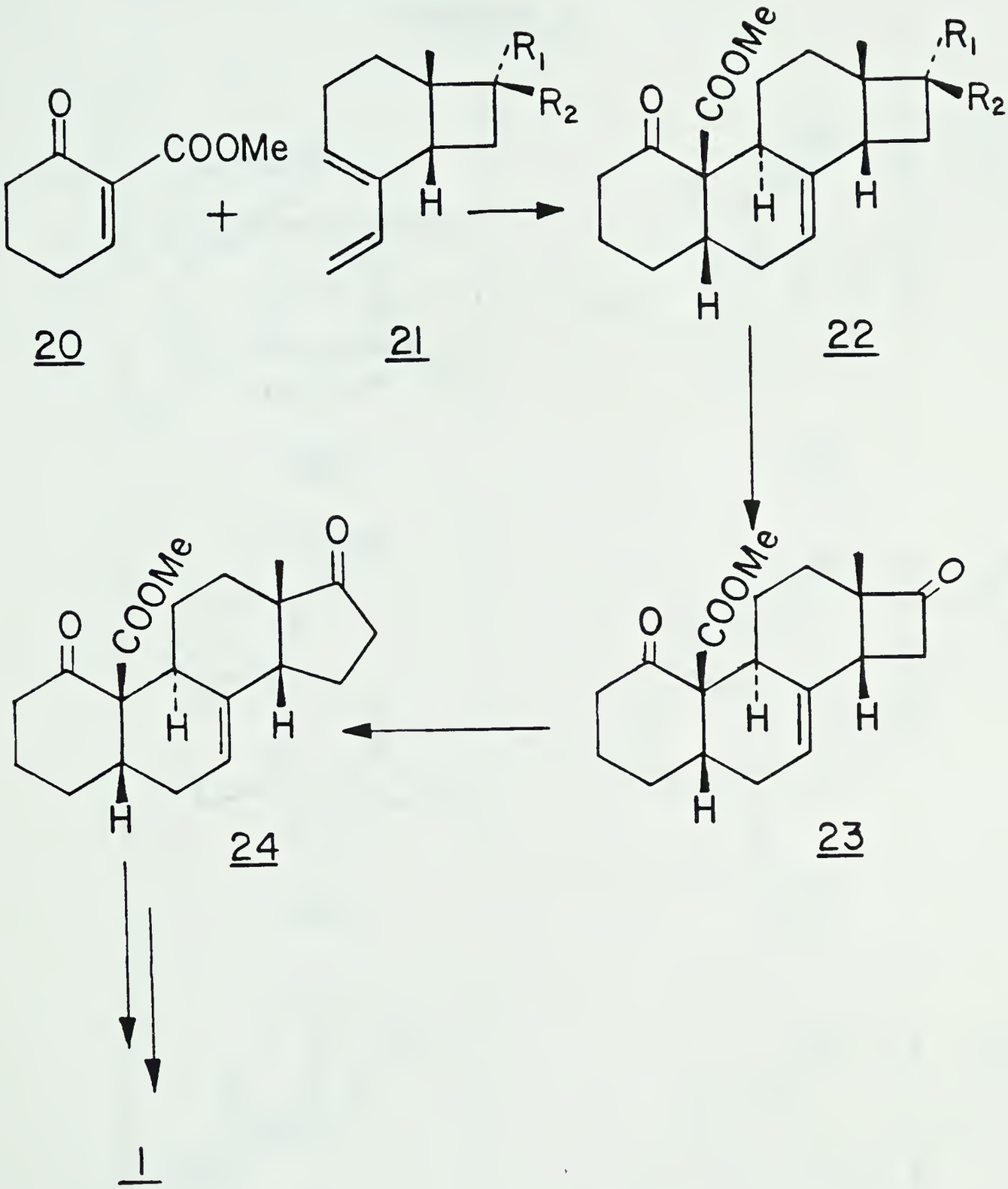


19

Scheme I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+
20
R1
R2
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21
COOMe
O
H
H
H
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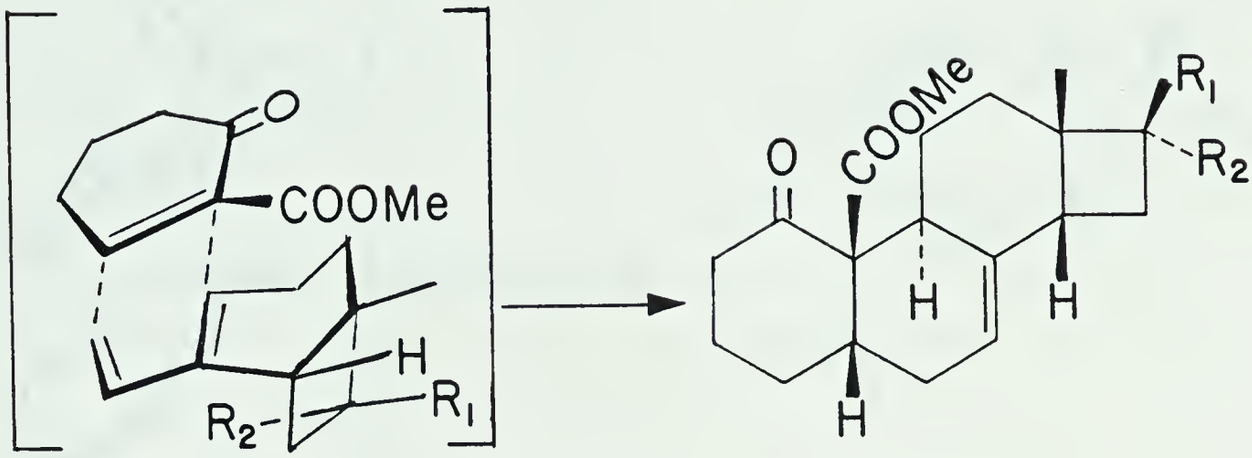
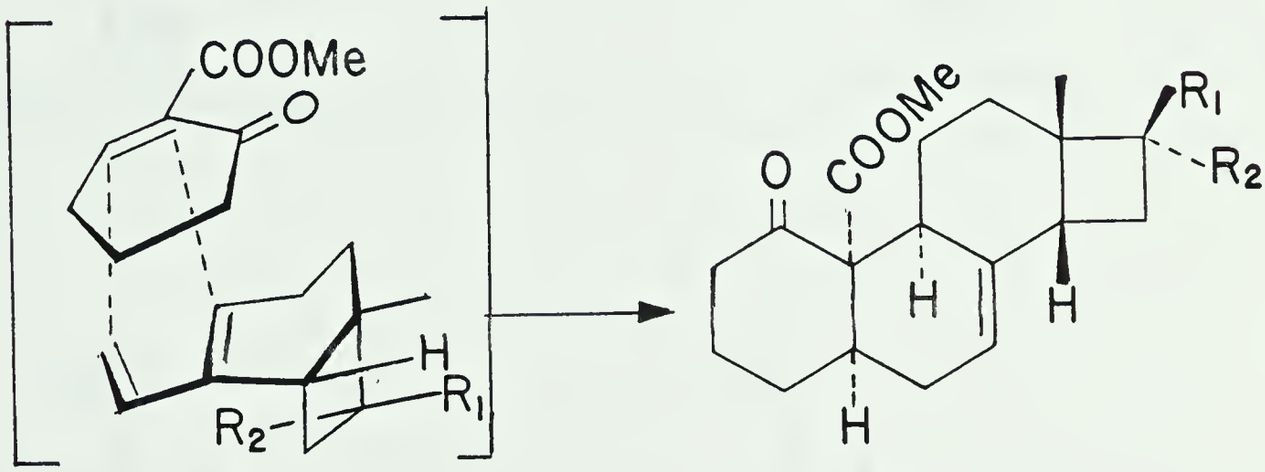
COOMe
O
O
H
H
H
23
COOMe
O
O
H
H
H
24
1

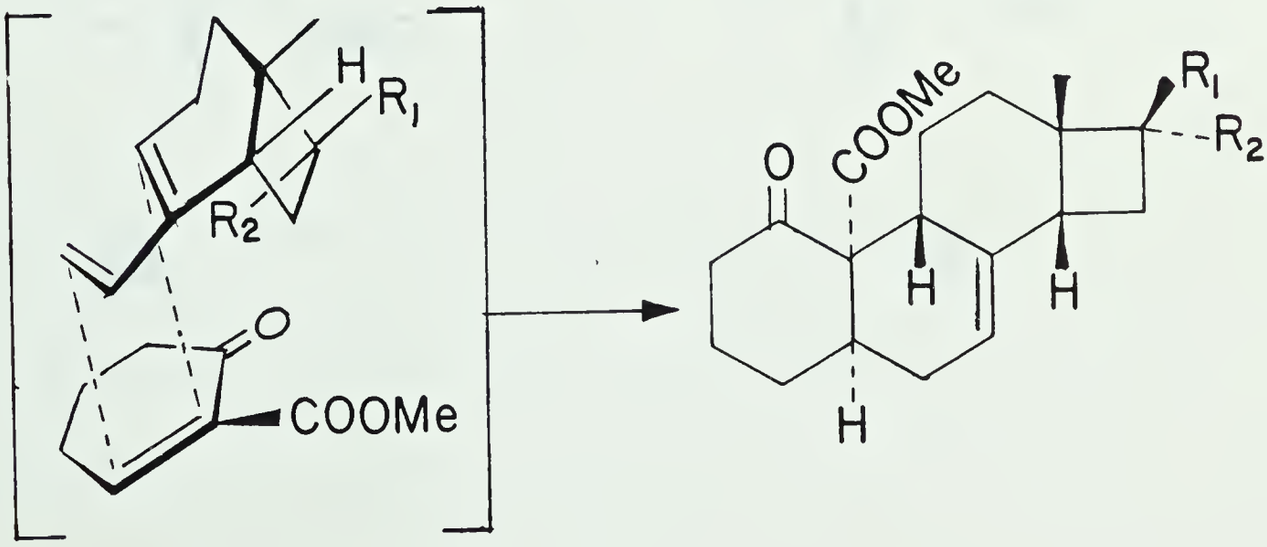
Scheme II



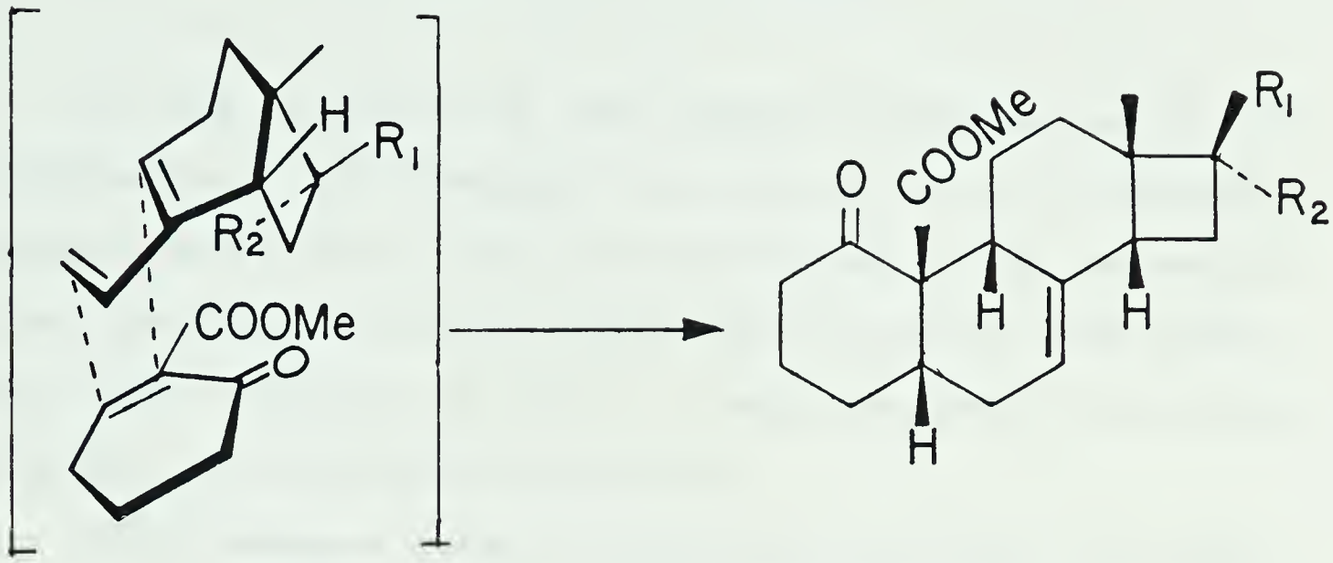
22a 22



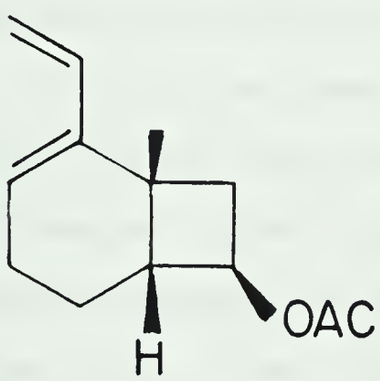
25a 25



26a 26



27a 27



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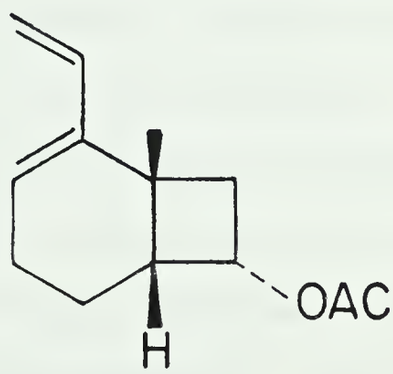

29

Results and Discussion

As the key step of the proposed synthetic study of strophanthidin (**1**) involved the coupling of the moderately complex diene **21** to the enone-ester **20**, it was essential that the diene **21** be available rapidly and in good yield. With this objective in mind, a rapid synthesis of **21** was proposed as outlined in Scheme III.

Vinyl acetate, being a cheap and commercially available compound was chosen as the olefin component. Irradiation of a solution of enone **30** and excess vinyl acetate in benzene[11] with a 450W Hanovia high-pressure mercury-vapor lamp using a pyrex filter for 48 h gave a yellow oil after removal of the solvent. The oily product contained at least five compounds as indicated by the presence of five methyl singlets around δ1.00 in the ^{1}Hmr spectrum of the crude material. The presence of five compounds indicated that stereo- as well as regio-isomers were formed.[9,11,12] However, in the photocycloaddition of an enone to vinyl acetate, it was expected that the head-to-tail photoadducts would be preferentially formed. It was therefore likely that the mixture would contain mainly the adducts with the desired regiochemistry and that they were mainly different in the stereochemistry at the three newly created asymmetric centers.

Equilibration of the trans ring junction to the thermodynamically more stable cis form[12] in the mixture of photoadducts should be easily accomplished by base treatment. This equilibration would give a less complex mixture which should be easier to purify. Towards this end, the mixture was treated with 1,5-diazabicyclo[4.2.0]undec-5-ene (DBU) in benzene at reflux. Interestingly, only two products in a ratio of 2:1 in 74% yield were isolated after the base treatment. They were subsequently analysed to have the structures **33** and **34**.* These photoadducts were separated by a combination of silica gel column chromatography and preparative high pressure liquid chromatography (HPLC).**

The major product which was faster moving by silica gel thin-layer chromatography (tlc) showed ir absorptions at 1737 and 1707 cm^{-1} for the presence of an ester and a ketone respectively. The presence of an acetate group was indicated by its ^{1}Hmr spectrum which showed a methyl singlet at δ2.09 as well as a triplet at δ4.91 (J = 8.0 Hz) due to

*The disappearance of the regioisomeric photoadduct(s) **35** was probably due to its conversion to the cyclobutene derivative **36** by a β-elimination and the opening of the cyclobutene ring of **36** under the reflux conditions to give the diene **37** which might have undergone further decomposition or could not be easily isolated.

**On a smaller scale (~6 g), flash chromatography could be used in a more rapid way to purify.

the methine proton adjacent to the acetate group. A singlet at δ1.26 was due to the angular methyl group.

The minor photoadduct which was obtained as white needles, m.p. 45-47°C, showed ir absorptions at 1733 and 1688 cm^{-1} for the presence of an ester and a ketone respectively. In the ^{1}Hmr spectrum, a singlet at δ2.10 was due to an acetate methyl and a triplet at δ4.74 was due to a methine proton adjacent to the acetate group. A singlet at δ1.30 was due to the angular methyl group.

A closer analysis of the spectral data suggested that the two products have the structures **33** and **34**, epimeric at the C-7 position only. The triplets at δ4.91 and 4.74 for the respective methine protons adjacent to the acetate group indicated that there are only two adjacent protons to each of these methine protons. The corresponding methine protons of the regioisomeric ketones **35** would have three adjacent protons and would be expected to show different splitting patterns.

Determination of the relative stereochemistry of these C-7 epimeric compounds should indicate which structure could be assigned to the major adduct and which structure could be assigned to the minor adduct. The ring junctions of both compounds could be readily assigned as <u>cis</u>, since it has been well established that in the bicyclo[4.2.0]octan-2-one systems having the <u>trans</u> ring junctions, epimerization with

base to the thermodynamically far more stable cis form can be easily effected.[12] The remaining stereochemistry at C-7 was determined on the basis of Nuclear Overhauser Enhancement (NOE) ^{1}Hmr experiments. These experiments have led to the assignments of structure **33** to the major photoadduct and structure **34** to the minor photoadduct.

In structure **34** where the angular methyl is cis to the methine proton at C-7, a large NOE effect would be observed for the methine proton on C-7 on saturation of the angular methyl group and vice versa, while in structure **33** where the angular methyl is trans to the methine proton at C-7, a negligible NOE effect would be observed for the methine proton on C-7 on saturation of the angular methine group and vice versa.

In the ^{1}Hmr spectrum of the major adduct, saturation of the angular methyl at δ1.26 gave an NOE effect of 1.5% for the methine proton on C-7 at δ4.71, while in the case of the minor adduct, saturation of the angular methyl at δ1.30 gave an NOE effect of 13.8% for the methine proton on C-7 at δ4.74. These observations are in accord with the assignments of the structure **33** to the major photoadduct and the structure **34** for the minor photoadduct.

The photocycloaddition of enone **30** to vinyl acetate was also done using acetonitrile as the solvent in the hope of improving the yield of photoadducts. However in changing to

a more polar medium, a lower yield of photoadducts was obtained (67%) and no significant changes to the ratio of adducts was observed (**33**:**34** = 2.4:1).

The ketones **33** and **34** were used for the preparations of the corresponding dienes **28** and **29** respectively. Treatment of a solution of ketone **33** in tetrahydrofuran at -78°C with vinyllithium gave two chromatographically separable alcohols in a ratio of ~3:1 in total yield of 66%. The major alcohol (faster moving by silica gel tlc) showed ir absorptions at 3480 and 1730 cm^{-1} due to an alcohol and an ester respectively. A M^+ - 18 peak of 206.1303 was observed in the mass spectrum. In the ^{1}Hmr, an ABX splitting pattern was observed at δ5,82, 5.11 and 4.89, indicating the presence of a terminal vinyl group. Methyl singlets appeared at δ1.93 and 0.92. A multiplet, at δ4.71 was due to the methine proton on the carbon bearing the acetate group.

The minor alcohol showed ir absorptions at 3460 and 1730 cm^{-1}, as well as a M^+ - 18 peak at 206.1305 in the mass spectrum. The ^{1}Hmr spectrum showed an ABX splitting pattern at δ5.96, 5.17 and 4.97. Methyl singlets appeared at δ1.92 and 1.09. A signal at δ4.47, appearing as a triplet (J = 8.0 Hz) was due to a methine proton adjacent to the acetate group.

Since the addition of vinyllithium was expected to occur mainly from the less hindered convex face of **33**, the major alcohol was assigned the structure **38** and the minor alcohol was assigned the structure **39**. As a dehydration of these alcohols to the diene **28** would destroy the stereochemistry of the newly created asymmetric center, no attempts were made to confirm the stereochemical assignments.

The major alcohol **38** was used to explore the preparation of the diene **28**. Treatment of **38** with p-toluenesulfonyl isocyanate in benzene at ~5% gave the carbamate derivative **40**. On purification of the crude carbamate by silica gel column chromatography, it led, much to our delight, to the required diene **28** in 60% yield. Also obtained, was a small amount of the carbamate **40** which could be pyrolysed[13] at 120-150°C under reduced pressure to give the diene **28** in 9% yield. In this way, the diene was isolated in combined yield of 69%.

The diene **28** showed ir absorptions at 1740 (ester), 1635 and 1600 cm^{-1} (both double-bonds). A molecular ion peak at m/e 206.1307 ($C_{13}H_{18}O_2$) in the mass spectrum of the diene was observed. The ^{1}Hmr spectrum displayed signals for the vinylic protons at δ6.25 as a doublet of doublets, at δ5.83 as a multiplet and at δ4.88 as a multiplet. Methyl singlets appeared at δ2.06 and 1.18.

The use of the minor alcohol **39** was not required as it was subsequently observed that the diene **28** could be prepared by a more rapid procedure as follows. Reaction of a solution of ketone **33** with 1.2 equivalent of vinyllithium (or 1.5 equivalent of vinylmagnesium bromide) in tetrahydrofuran at -78°C gave the epimeric alcohols **38** and **39** which, without isolation, were reacted with p-toluenesulfonyl isocyanate at 0°C. After the work-up, the resulting carbamate derivatives **40** and **41** were pyrolysed[13,14] in a Kuhrgelrohr distillation apparatus at 120-150°C under reduced pressure (~1.0 torr) to give the pure diene **28** in 65% overall yield.

The same sequence of reactions could also be applied to the isomeric photoadduct **34** for the preparation of the corresponding diene **29**. However, in order to obtain the best overall yield of 58%, a work-up after the formation of the intermediate alcohols was required.

In order to explore the reactivity of the dienes, as well as the "facial" selectivity of the Diels-Alder reactions, the additions of the dienes **28** and **29** to p-benzoquinone were initially examined. Reaction of a solution of diene **28** and 1.2 equivalent of p-benzoquinone in methylene chloride at -33°C and under stannic chloride catalysis gave an adduct **42** which decomposed readily on exposure to air and thus, could not be easily purified. To

facilitate the isolation of the product, the triacetate derivative **43** was prepared. This was achieved by immediate treatment of the crude Diels-Alder adduct **42** with acetic anhydride and N,N-dimethylaminopyridine. The resulting triacetate derivative **43** was obtained in 71% overall yield. It showed a molecular ion peak at m/e 398.1734 ($C_{23}H_{26}O_6$) in the mass spectrum, as well as ir absorptions at 1762 and 1730 cm^{-1}. The ^{1}Hmr spectrum showed methyl singlets at δ2.36 and 2.29, each due to an aromatic acetate group. The remaining methyls appeared at δ2.10 and 0.99, each as a singlet. Two multiplets at δ4.73 and 3.45 were assigned to a proton each on C-16 and C-9* respectively. The stereochemistry of the newly created asymmetric center at C-9 (relative to the other three centers at C-13, C-14 and C-16) was assigned based on an ^{1}Hmr nuclear overhauser enhancement (NOE) experiment. It was observed that saturation of the signal at δ4.73 (C-16 H) led to an NOE effect of 4.0% on the signal at δ3.45 (C-9 H).** An NOE effect can only be observed when the protons on C-9 and C-16 are <u>cis</u> to each other. Thus, the triacetate derivative must have the relative stereochemistry as depicted in structure **43**.

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*The nomenclature used for this compound and other tetracyclic compounds in this study, is based on the parent estrane ring system **44** with the numbering as depicted.

**Conversely, saturation of signal at δ3.45, led to an NOE effect of 3.2% on the signal at δ4.73.

The Diels-Alder addition of the isomeric diene **29** with 1.5 equivalent of p-benzoquinone proceeded at -33°C and under stannic chloride catalysis to give the unstable dihydroxy compound **45** which could not be purified. Again, to facilitate the isolation of product, the corresponding triacetate derivative **46** was prepared employing acetic anhydride and N,N-dimethylaminopyridine as the base. The resulting triacetate **46** which was obtained in 57% overall yield showed ir absorptions at 1763 and 1735 cm^{-1}. A molecular ion peak at m/e 398.1735 ($C_{23}H_{26}O_6$) was observed in the mass spectrum. The ^{1}Hmr spectrum showed methyl singlets at δ2.38 and 2.32, each due to an aromatic acetate group. The remaining methyl singlets appeared at δ2.08 for another acetate group and at δ1.17 for the angular methyl. A multiplet at δ5.56 was due to the vinylic proton.

It was confirmed that the triacetate **46** was only epimeric to the other triacetate **43** at the C-16 carbon by a series of chemical transformations as depicted in Scheme IV. The dimethyl ether **47** was obtained by methylation of the Diels-Alder adduct **42** with methyl iodide and potassium carbonate in refluxing acetone. Treatment of **47** with potassium carbonate in aqueous methanol furnished the alcohol **48** which was converted into the cyclobutanone derivative **51** by Swern's oxidation.[15] Compound **51** showed an ir absorption at 1776 cm^{-1}, corresponding to the presence of

the four-membered ring ketone. A molecular ion peak at m/e 298.2567 corresponding to the chemical formula $C_{17}H_{22}O_3$ was observed in the mass spectrum. The ^{1}Hmr spectrum showed two doublets at δ6.54 and 6.56 due to the two aromatic protons. Methyl singlets appeared at δ3.71 and 3.69, each due to a methyl ether, as well as at δ1.13 for the angular methyl group. A multiplet at δ5.66 was due to the vinylic proton.

A similar series of reactions was applied to the epimeric dimethyl ether **49** which was prepared from the Diels-Alder adduct **45**. Removal of the acetate group of **49** gave the alcohol **50**. Oxidation of the alcohol **50** led to a cyclobutanone derivative which was found to be identical in spectral properties (^{1}Hmr, ^{13}Cmr and ir), as well as tlc behaviour to the cyclobutanone **51**, obtained previously from the dimethyl ether **47** (vide supra).

Thus, the additions of the diene **28** and **29** to p-benzoquinone under stannic chloride catalysis, led to the formation of the C-16 epimeric adducts **42** and **45**, respectively. These adducts were each formed by the exclusive addition of p-benzoquinone to the less hindered convex face of the diene via the transition states **42a** and **45a** as shown in Scheme V. These results suggested that a profound "facial" selectivity in favor of the addition of the dienophile to the less hindered convex face of each of

the dienes **28** and **29** could indeed be effected. This "facial" selectivity resulted in the formation of a trans relationship between the methine proton on C-9 and the angular methyl on C-13 in adducts **42** and **45**. A trans relationship between these centers would give the required stereochemistry for strophanthidin synthesis.

It is worth noting that the resulting D-nor-steroids **43** and **46** may have some interesting biological activities.* By the use of the Diels-Alder approach, these D-nor-steroids which would otherwise be difficult to prepare by other routes, could be prepared in high yield by a short sequence of reactions. Compound **43** was prepared in four steps from the ketone **33** in 49% overall yield, while the epimeric compound **46** was prepared similarly from the ketone **34** in 33% overall yield.

Having established that the required "facial" selectivity could be effected in the required direction, the Diels-Alder additions of enone-ester **20** with the dienes **28** and **29** were examined.

Addition of the diene **28** to 3.0 equivalent of enone-ester **20** proceeded at -33°C and under stannic chloride catalysis to give a ~1:1:1 mixture (by ^{1}Hmr analysis) of three adducts, designated as **Ia**, **Ib** and **Ic** in 78% yield.

*The biological activities of the adduct **43** is under current examination.

After careful chromatographic purification, two fractions were obtained, one containing only pure **Ic** and the other contained a mixture of **Ia** and **Ib.** Adduct **Ic** showed ir absorptions at 1736 and 1718 cm^{-1} indicating the presence of an ester and a ketone respectively. A molecular ion peak at m/e 360.1955 in the mass spectrum gave a chemical formula of $C_{21}H_{28}O_3$ for the adduct. The ^{1}Hmr spectrum showed a multiplet at δ5.35 for a vinylic proton, as well as another multiplet at δ4.86 for the methine proton adjacent to the acetate group. Methyl singlets appeared at δ3.76, 2.10 and 0.98.

The mixture **Ia** and **Ib** showed a molecular ion peak at m/e 360.1985, in the mass spectrum. The ir spectrum showed ester and ketone carbonyl absorptions at 1735 and 1716 cm^{-1}. The ^{1}Hmr spectrum showed two sets of signals in an integral ratio of ~1:1. Two sets of methyl singlets, due to a methyl ester (δ3.82 and 3.74), an acetate group (δ2.21 and 2.04) and the angular methyl (δ1.17 and 1.07), were observed.

The spectral data indicated that the three adducts must be isomeric and must be stereoisomeric and/or regioisomeric to each other. The presence of regioisomers was tentatively ruled out, since for a 1,2-disubstituted diene, the <u>ortho</u>-rule would operate in the Diels-Alder addition. As a working hypothesis, the presence of only stereoisomers was

considered for the subsequent discussions. Each of these adducts could thus be assigned to any of the diastereomeric keto-esters represented by structure **52**.*

The mixture of adducts **Ia** and **Ib** could be further separated as follows. Treatment of the mixture with potassium carbonate in aqueous methanol at room temperature gave the chromatographically separable alcohols **IIa** and **IIb**, respectively, in combined yields of 84%. The adduct **Ic** was similarly converted to the corresponding alcohol **IIc**. Each of these alcohols could be any of the diasteromeric alcohols as represented by structure **53** which was derived from structure **52** with retention of configuration.

Spectral analysis again indicated that they are isomeric to each other. Attempts were made, at this stage, to determine the relative stereochemistry of each alcohol. Several ^{1}Hmr NOE experiments were performed on each alcohol. Of these NOE experiments attempted, the result of only one experiment involving the alcohol **IIc** could be interpreted conclusively. It was observed that saturation of the signal for the methine proton on C-9 at δ3.00 led to an NOE effect of 4.2% on the proton at C-16. This observation established the <u>cis</u> relationship between the

*The <u>cis</u>-principle for the Diels-Alder addition required that the carbomethoxy group and the methine proton at C-5 must be <u>cis</u> for these three adducts.

protons on C-9 and C-16. Thus, the alcohol **IIc** must have the proton on C-9 trans to the angular methyl at C-13 as depicted in structure **54**.

Alcohol **54** could be further converted to the cyclobutanone derivative **55** by Jone's oxidation[16] in 73% yield. The crystalline cyclobutanone derivative (m.p. 142-144°C) has been submitted for an X-ray analysis in order to determine its structure conclusively.

The Diels-Alder reaction of enone ester **20** with the diene **29** was also examined. The addition again proceed smoothly at -33°C and under stannic chloride catalysis to give an inseparable ~1:1:0.3 mixture of three adducts designated as **56a**, **56b** and **56c**. A cis stereochemistry for the A/B ring junction for each Diels-Alder adduct is required on the basis of the cis-principle in 68% yield. No attempts were made to separate these compounds. They were however shown to have the same relative stereochemistry with respect to the centers at C-5, C-9 and C-10, to the previous Diels-Alder adducts **Ia**, **Ib** and **Ic** by the transformations as illustrated in Scheme VI. The mixture of Diels-alder adducts **Ia**, **Ib** and **Ic** was converted into the 1:1:1 mixture of cyclobutanones **58** by hydrolysis of the acetate group ($K_2CO_3/MeOH/H_2O$) and oxidation (Swern's oxidation)[15] in 72% overall yield. The mixture of cyclobutanones **58** showed ir absorptions at 1775, 1740 and 1716 cm^{-1} as well as a

molecular ion peak at m/e 316.1676 ($C_{19}H_{25}O_4$) in the mass spectrum. The ^{1}Hmr spectrum showed three sets of signals in an integral ratio of ~1:1:1. One set was similar to those of the cyclobutanone **58** prepared previously. The other two sets showed multiplets at δ5.50 and 5.38 for the vinylic proton. Two sets of methyl singlets appeared at δ3.80 and 3.73 for the methyl ester and at δ1.27 and 1.11 for the angular methyl.

A similar transformation of the other series of Diels-Alder adducts **56a**, **56b** and **56c** was again carried out (Scheme VI). It led to a 1:1:0.3 mixture (by ^{1}Hmr integration) of cyclobutanones **58**. Thus, the two series of Diels-Alder adducts must be epimeric to each other at the carbon center bearing the acetate group. It should be noted that the cyclobutanone **55** obtained from the other series was found to be identical to one of the major adducts in the 1:1:0.3 mixture of **58**.

Although the Diels-Alder additions gave good yields of adducts in both series, the required stereoselectivity needs to be improved. As noted in the introduction, the Diels-Alder additions of the dienes **28** and **29** could in each case proceed through the four transition states **22a**, **25a**, **26a** and **27a** (Scheme II). As only three Diels-Alder adducts were obtained in each series, therefore one of these transition states could be ruled out. The results of the additions to

p-benzoquinone clearly suggested that the transition state **27a** (resulting from addition by secondary overlap with the ketone carbonyl of **20** and from the more hindered concave face of the diene) would be disfavored. Therefore, the Diels-Alder additions of the dienes **28** and **29** to the enone-ester **20** most likely proceed through the transition states **22a**, **25a** and **26a** to give the adducts **22**, **25** and **26**, with the stereochemistry as indicated. Adduct **22** is required for the strophanthidin synthesis. Since the Diels-Alder reaction of enone-ester **20** is known to occur predominantly by addition of a diene endo to the ester group of **20** (see Chapter 1) it was therefore probable that products of structure **22** (see Scheme I) were formed as one of the major adducts in both series. Considering the complexity of the structures, the total yield of the required adducts **22** that were obtained from both series, was reasonably useful synthetically.*

The observations made in this study indicated that the required adducts **22** could be obtained in synthetically useful yield. However, a much higher stereoselectivity in favor of **22** would be desirable not only because an increased yield would improve the overall efficiency of this synthetic goal, but also the purification of the Diels-Alder adducts

*A calculation based on the product ratios and the yields, gave an average yield of 27% for the adducts of structural type **22**.

may be greatly simplified.*

Another observation made in this study showed that there was a change in stereoselectivity in changing from the diene **28** to **29.** The endo disposition of the acetate group of the diene **29** would be expected to increase the steric hindrance to its concave face, thereby favoring more of addition from the less hindered convex face. In this regard the results obtained, suggested that the ~1:1:0.3 mixture of adducts **56a**, **56b** and **56c** would consist of only a small amount of the product arising from the addition from the concave face. It is therefore probable that the minor component in the mixture was due to addition via the transition state **26a** to give the undesirable adduct **26.** Therefore, by increasing the steric bulk of the R_1 group of the diene **21** (Scheme II), the facial selectivity could be improved.

If the "facial" stereoselectivity in favor of the addition from the less hindered convex face of the diene **21** could be improved**, then, the next task of improving the

*The ability to separate the adducts **Ia**, **Ib** and **Ic** via their alcohols **IIa**, **IIb** and **IIc** of one series indicated that purification of the required adducts is not a difficult problem.

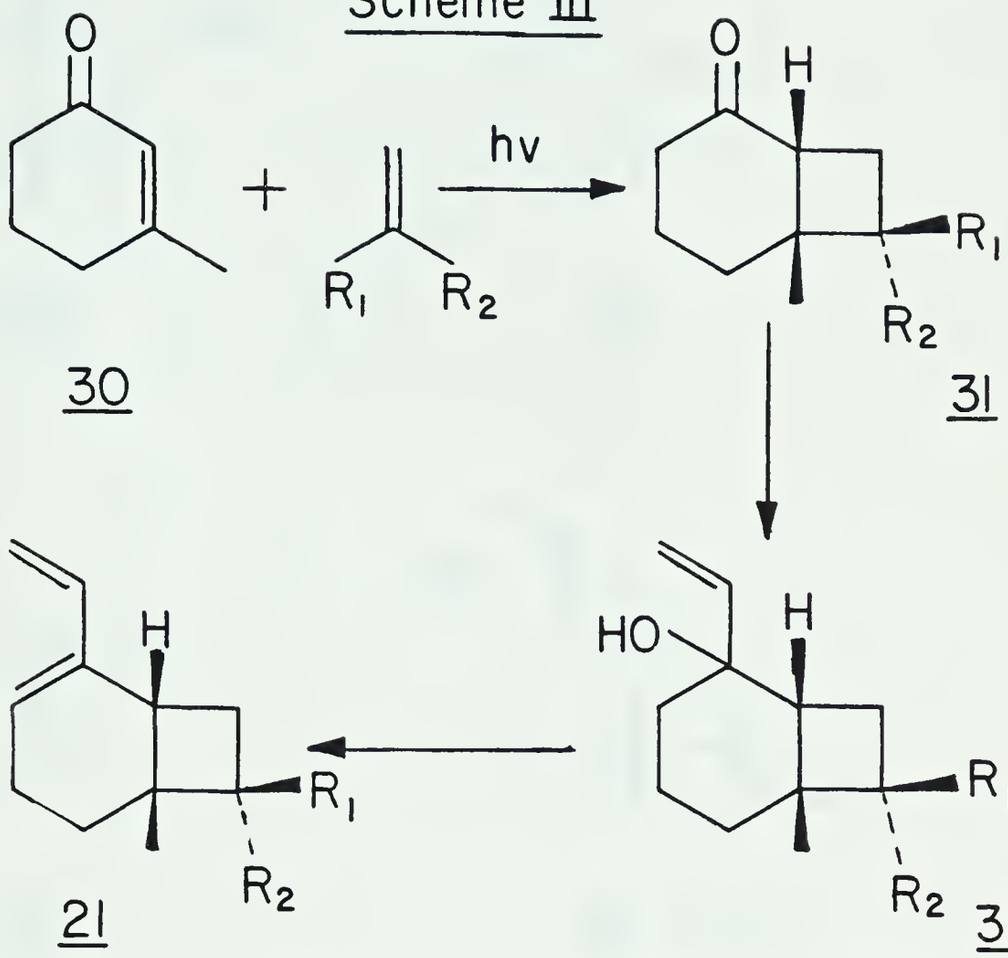
Another way of improving this "facial" selectivity would be to use a dienophile such as **59 which should further enhance the addition from the less hindered convex face of the diene **21.**

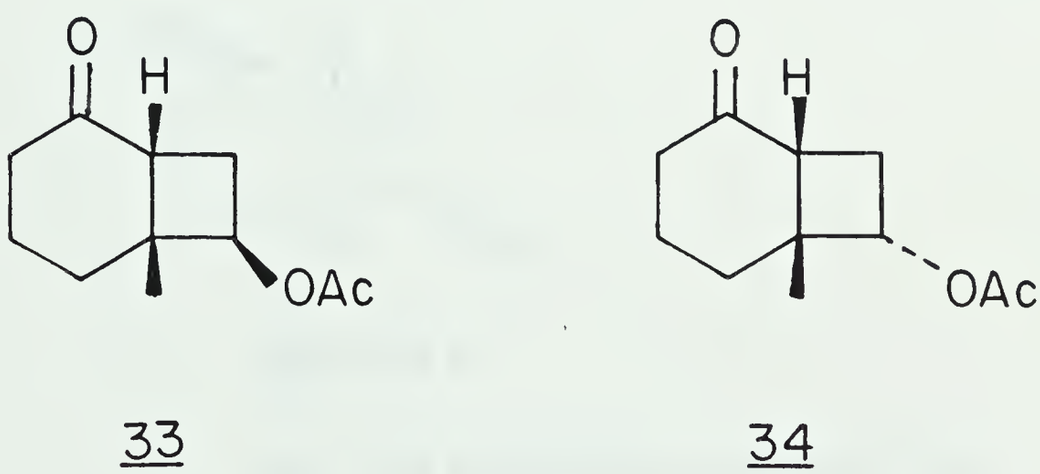
endo selectivity in favor of the addition via transition state **22a** (in competition with transition state **25a**) to give the required adduct **22** could be improved by the introduction of a bulky substituent at the 3-position of the diene moiety of **21**.*

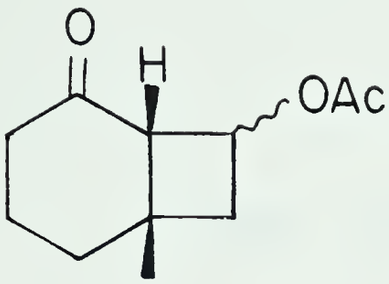
As a prerequisite for pursuing these objectives just discussed, the structural elucidations most notably, of the desired adducts in both series, are required and the successful outcome of the X-ray analysis of the cyclobutanone derivative **55** will facilitate the work in this direction.

*It was observed that introduction of a more bulky substituent at the 3-position of a 1,3-disubstituted diene led to enhanced addition of diene endo to the ester group of **20** (see Chapter 1 and 2).

Scheme III







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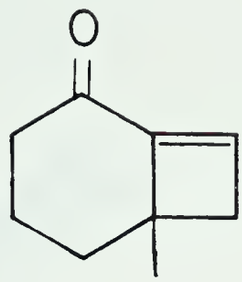

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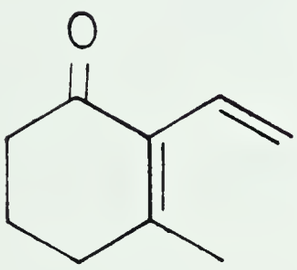

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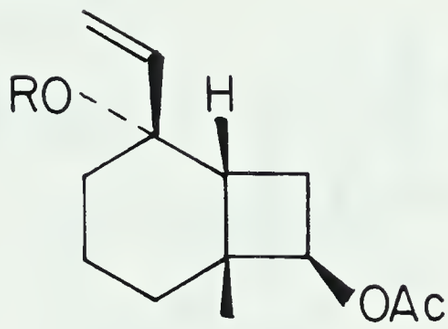
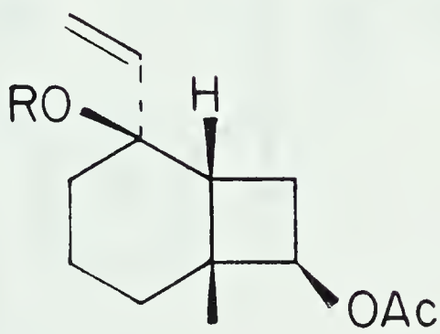


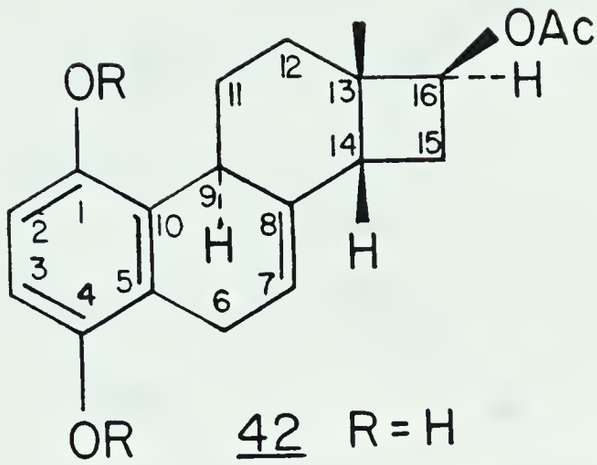
38 R = H

40 R = $CONHSO_2$-p-$C_6H_5CH_3$



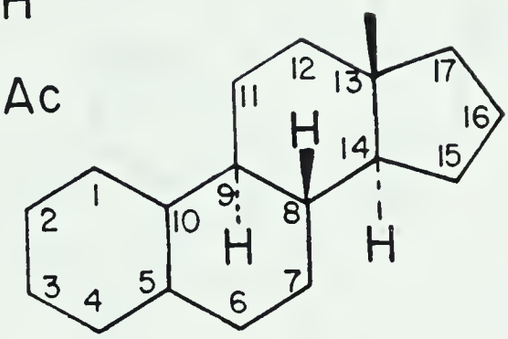
39 R = H

41 R = $CONHSO_2$-p-$C_6H_5CH_3$



42 R = H

43 R = Ac



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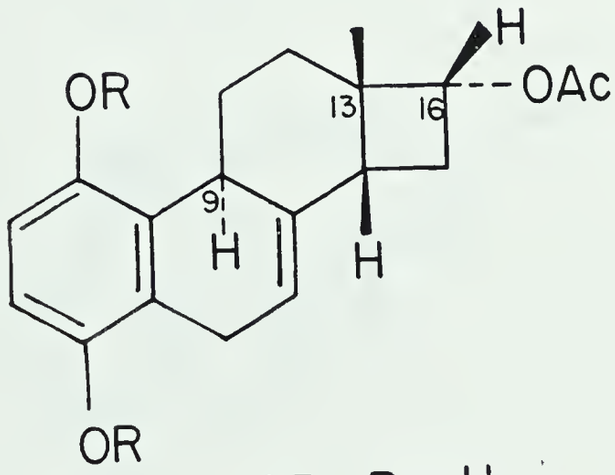
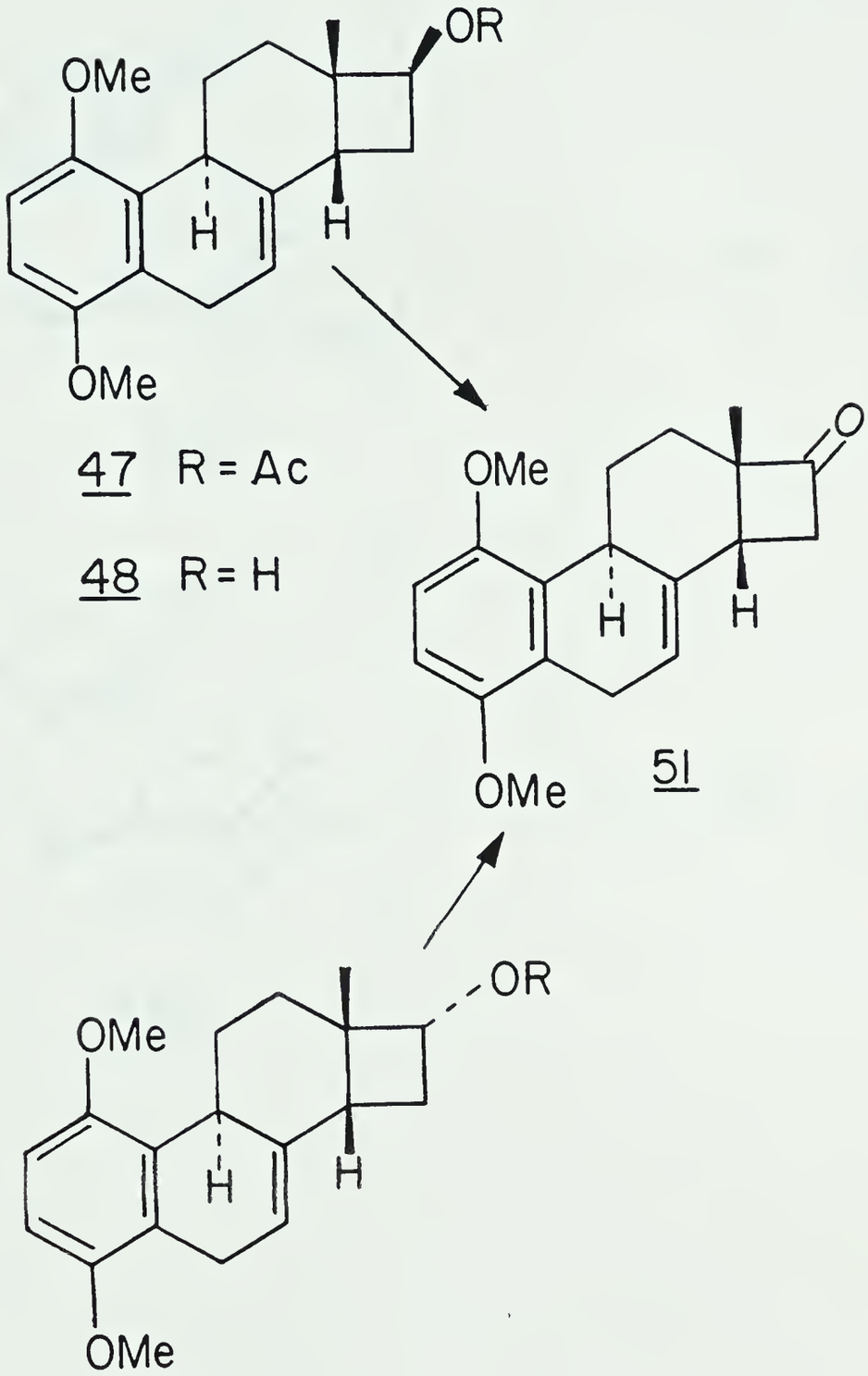


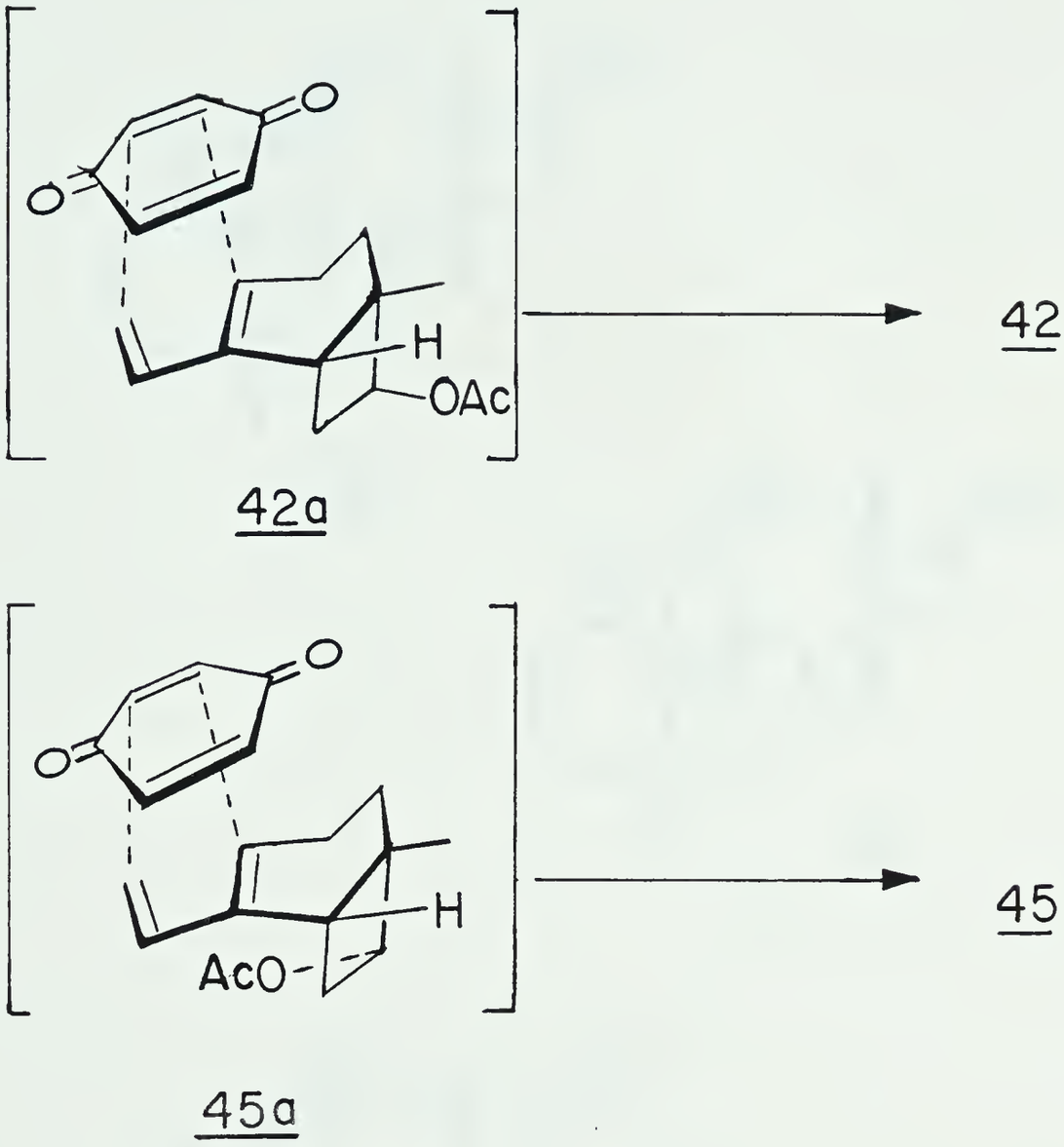
45 R = H

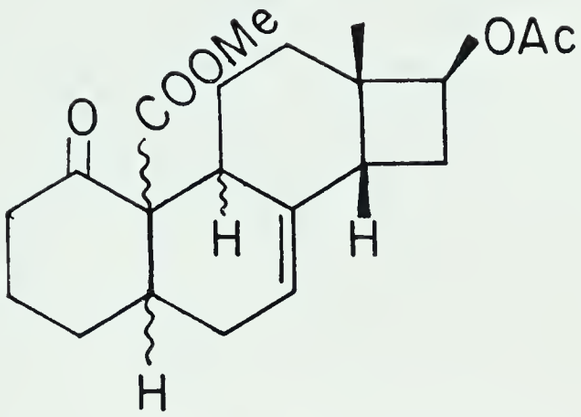
46 R = Ac

Scheme IV



Scheme V





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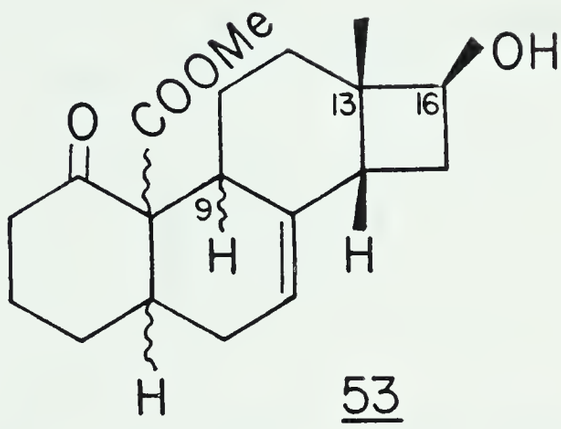

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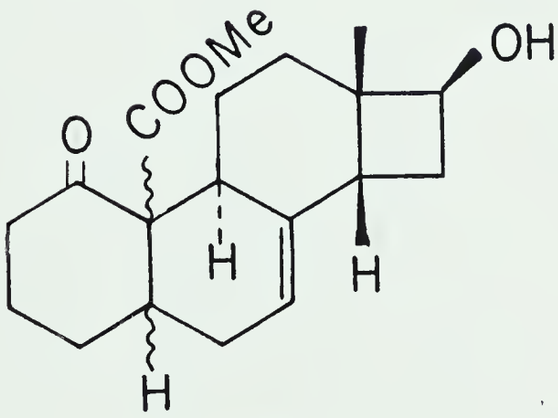

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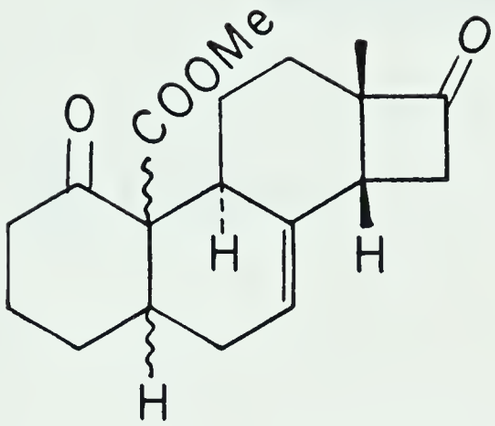

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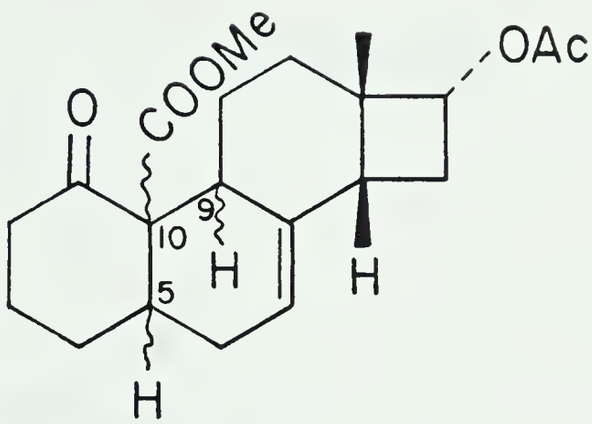
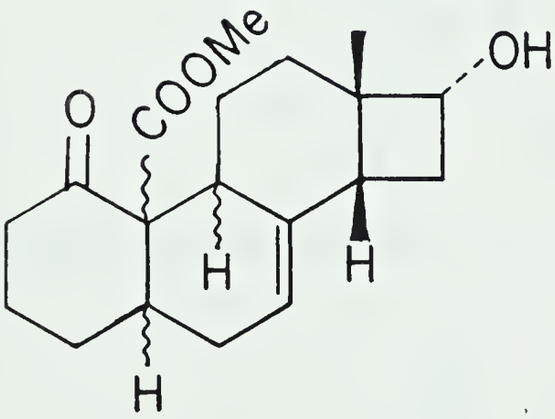
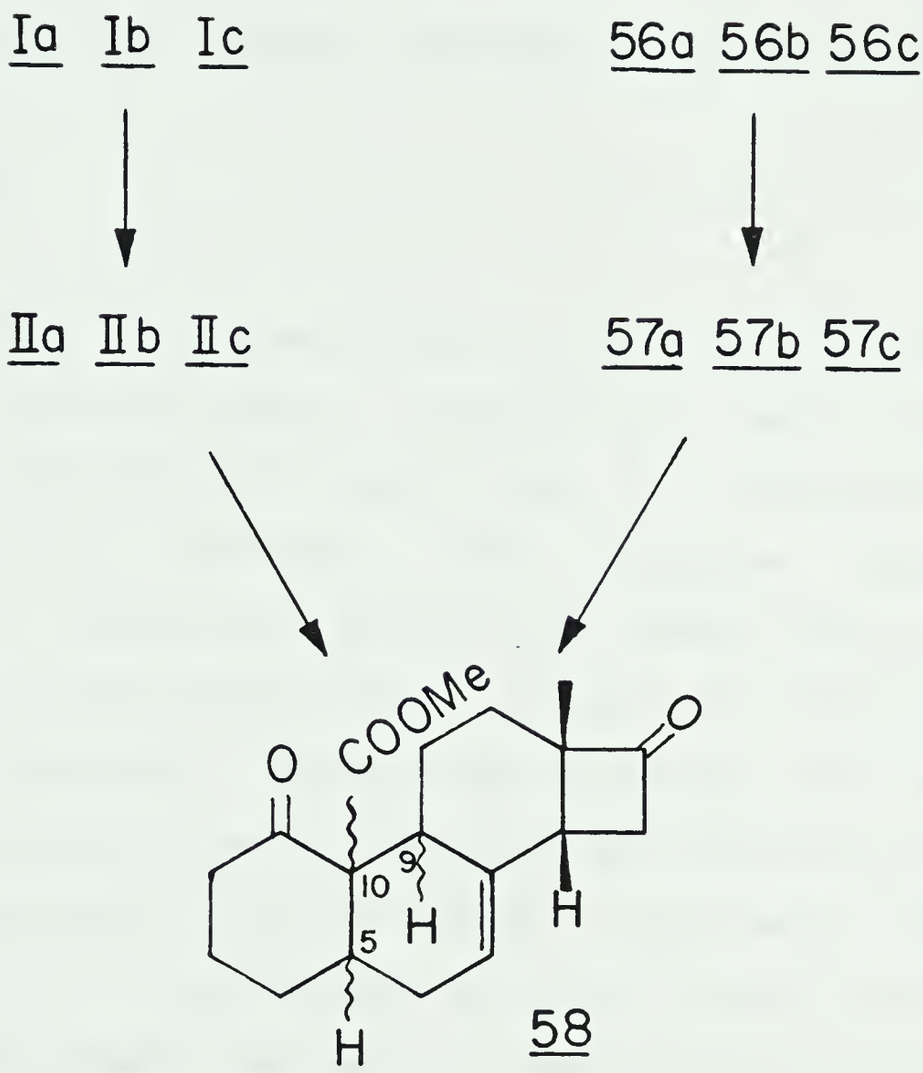


56a, 56b, 56c,



57a, 57b, 57c,

Scheme VI



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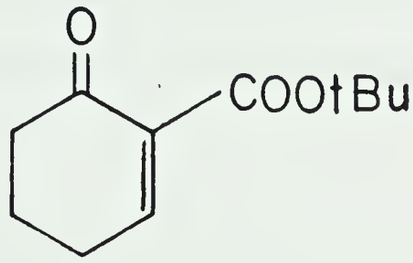

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Experimental

General

For general remarks, see Chapter 1 of this thesis.

Materials

Benzene and tetrahydrofuran were freshly distilled over lithium aluminium hydride. Triethylamine was distilled over calcium hydride and stored over 3 Å molecular sieve. Acetone was distilled over potassium permanganate crystals. Methylene chloride was washed with an equal volume of 10% aqueous sodium carbonate and distilled over calcium chloride. Methanol was distilled over magnesium metal. *n*-Hexane was purified by simple distillation for use in chromatographic purifications. Nitrogen or argon was passed over a purification train of Fieser's solution,[17] saturated aqueous lead acetate, concentrated sulfuric acid and potassium hydroxide pellets. Enone-ester **20**[16,17] was prepared from 2-carbomethoxycyclohexanone according to the procedure described in Chapter 1 of this thesis.

7β-Acetoxy-6β-methyl-1β-bicyclo[4.2.0]octan-2-one (**31**) and 7α-acetoxy-6β-methyl-1β-bicyclo[4.2.0]octan-2-one (**32**)*.

a) Using Benzene as the Solvent.

The apparatus used for the photocycloaddition is shown diagrammatically in Fig. 1 (p. 231). 3-Methyl-2-cyclohexen-1-one (**30**) (15 g, 0.14 mol) and vinyl acetate (117 g, 1.36 mol) were placed in benzene (700 mL) in the reaction vessel. The reaction mixture was kept agitated by a constant flow of nitrogen throughout the reaction period. Shortly, after filling up the Dewar flask with crushed ice and water, the solution was irradiated with a 450W Hanovia high pressure mercury-vapor quartz lamp using a pyrex filter. After 48 h the reaction mixture was concentrated.

The resulting yellow viscous oil was dissolved in benzene (300 mL). 1,5-Diazbicyclo[5.4.0]undec-5-ene (20.7 g, 0.14 mmol) was added and the resulting mixture heated to reflux. After 49 h the reaction mixture was cooled to room temperature and concentrated. Column chromatography of the residue, eluting with 2-5% ether in n-hexane gave pure ketone **33** (7.27 g, 27.3% yield) as a colorless oil: ^{1}Hmr δ4.91 (t, 1H, J = 8.0 Hz, -CH-O-), 2.09 (s, 3H, $-OCOCH_3$) and

*The stereochemical designations used for all the chemical names in this section denote relative stereochemistry. All compounds used and obtained were racemic.

1.26 (s, 3H, $-C-CH_3$); ir (film) 1737 (ester C=O)) and 1707 cm^{-1} (ketone C=O); ms m/e 136.0889 (M^+ - 60; Calcd. for $C_9H_{12}O$: 136.0889) and ms m/e 111.0812 (M^+ - 85; Calcd. for $C_7H_{11}O$: 111.0810).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.28.

Continued elution with 5% ether in n-hexane gave a mixture of ketones **33** and **34** (8.34 g, 31.2% yield) in a ratio of 4:1 (by ^{1}Hmr analysis). This mixture could be separated by preparative high pressure liquid chromatography on a Water Associates Prep LC/system 500 using a silica gel cartridge and eluting with 30% ethyl acetate in n-hexane. Fractions were collected by shaving the leading and trailing edges of the broad peak and recycling of the central position. The combined "leading edges" fractions were concentrated to give pure ketone **33** (6.6 g). The "trailing edges" fractions were combined and concentrated to give the isomeric ketone **32** (1.3 g). A single recrystallization from n-hexane gave white crystals of pure ketone **34**, m.p. 45-47°C.

Continued elution from the silica gel column, with 5-10% ether in n-hexane gave white crystals of pure ketone **34** (4.41 g, 16.5% yield): ^{1}Hmr δ4.74 (t, 1H, J = 8.0 Hz, -CH-O-), 2.10 (s, 3H, $-OCOCH_3$) and 1.30 (s, 3H, $-C-CH_3$); ir 1733 (ester C=O) and 1688 (ketone C=O); ms m/e 136.0666 (M^+

- 60; Calcd. for $C_9H_{12}O$: 136.0889) and ms m/e 111.0818 (M^+ - 85; Calcd. for $C_7H_{11}O$: 111.0810).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.19; H, 8.34.

b) Using Acetonitrile as the Solvent.

Using the photochemical apparatus as depicted in Fig. 1 (p. 231), a solution of 3-methyl-2-cyclohexen-1-one (**30**) (4.87 g, 44.2 mmol) and vinyl acetate (38.1 g, 0.44 mmol) in acetonitrile (180 mL) was photolysed with a 450W Hanovia high pressure mercury vapor quartz lamp using a pyrex filter. After 43 h the light source was shut-off and the reaction mixture concentrated. The resulting viscous yellow oil was dissolved in benzene (80 mL) and 1,5-diazabicyclo[5.4.0]undec-5-ene was added. The reaction mixture was heated to reflux under an atmosphere of argon for 46 h. After cooling to room temperature, the solution was concentrated. The resulting dark pink colored oil was purified by flash chromatography on silica gel. Elution with 10% ethyl acetate in n-hexane gave pure ketone **31** (4.1 g, 47.2% yield) as a colorless oil. Continued elution gave the isomeric ketone **32** (1.71 g, 19.7% yield). Recrystallization from n-hexane gave white crystals of pure ketone **32**, m.p. 45-47°C.

7β-Acetoxy-2β-(1-ethylene)-6β-methyl-1β-bicyclo[4.2.0]octan-2-ol (**38**) and 7β-Acetoxy-2α-(1-ethylene)-6β-methyl-1β-bicyclo[4.2.0]octan-2-ol (**39**).

To a solution of ketone **31** (3.55 g, 18.1 mmol) in tetrahydrofuran (60 mL at -78°C and under an atmosphere of nitrogen, was added a solution of vinyllithium (13.9 mL of 1.3 M, 18.1 mmol) in tetrahydrofuran. After stirring for 3 h ice-cold water was added to destroy excess vinyllithium. Saturated aqueous ammonium chloride was added. The resulting mixture was extracted with ether. The organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with a solution of 15% ethyl acetate in n-hexane gave the alcohol **38** (1.95 g, 47.5% yield): ^{1}Hmr δ5.82 (dd, 1H, J = 19 Hz, J' = 10.5 Hz, -C<u>H</u>=CH_2), 5.11 (dd, 1H, J = 19Hz, J' = 2.0 Hz, -CH=CH<u>H</u>), 4.71 (m, 1H, -CH-O-), 1.93 (s, 3H, -$OCOCH_3$) and 0.92 (s, 3H, -C-CH_3); ir (film) 3480 (-OH) and 1730 cm^{-1} (C=O); ms m/e 206.1303 (M^+ - 18; Calcd. for $C_{13}H_{18}O_2$: 206.1307). Continued elution gave another isomeric alcohol **39** (742 mg, 18.3% yield): ^{1}Hmr δ5.96 (dd, 1H, J = 19 Hz, J' = 10 Hz, -C<u>H</u>=CH_2), 5.17 (dd, 1H, J = 19 Hz, J' = 2.0 Hz, -CH=CH<u>H</u>), 4.97 (dd, 1H, J = 10 Hz, J' = 2.0 Hz, -CH=C<u>H</u>H), 4.47 (t, 1H, J = 8.0 Hz, -CH-O-), 1.92 (s, 3H, -$OCOCH_3$) and 1.09 (s, 3H, -C-CH_3); ir (film)

3460 (-OH) and 1730 cm^{-1} (C=O); ms m/e 206.1305 (M^+ - 18; Calcd. for $C_{13}H_{18}O_2$: 206.1307).

7β-Acetoxy-2(1-ethylene)-6β-methyl-1β-bicyclo[4.2.0]oct-2-ene (**28**).

p-Toluenesulfonyl isocyanate (592 mg, 3.0 mmol) was added to a solution of alcohol (**39**) (610 mg, 2.7 mmol) in benzene at ~5°C. After stirring for 3 h, ice-cold water was added to destroy excess isocyanate. The layers were separated and the aqueous phase was extracted with ether. The organic solutions were combined, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ether in *n*-hexane gave the pure diene **28** (386 mg; 60% yield) as a colorless oil: ^{1}Hmr δ6.18 (dd, 1H, J = 17.5 Hz, J' = 10.5 Hz, -C*H*=CH_2), 5.74 (m, 1H, -C=CH-), 4.88 (complex m, 3H, -CH=C*H*$_2$ and -C*H*-O-), 1.98 (s, 3H, -$OCOCH_3$); ir (film) 1742 (C=O), 1635 (C=C) and 1600 cm^{-1} (C=C); ms M^+ 206.1301 (Calcd. for $C_{13}H_{18}O_2$: 206.1307). Continued elution with 20-50°C ether in *n*-hexane gave an impure fraction containing the carbamate derivative **40** (25 mg) which was pyrolysed at 120-150°C under reduced pressure (~1.0 torr) to give the pure diene **28** (51 mg; 9% yield) after column chromatography of the distillate on silica gel, eluting with 10% ether in *n*-hexane.

7β-Acetoxy-2(1-ethylene)-6β-methyl-1β-bicyclo[4.2.0]oct-2-ene (**28**).

At -78°C to a solution of ketone **33** (2.73 g, 13.9 mmol) in tetrahydrofuran (40 mL), was added vinylmagnesium bromide (15 mL) of 1.0 M, 15.0 mmol). After allowing the temperature of the dry-ice/acetone bath to warm to 0°C, *p*-toluenesulfonyl isocyanate (3.5 g, 17.8 mmol) was added. After stirring for 1 h at 0°C, ice-cold water was added to destroy excess isocyanate. A solution of aqueous saturated ammonium chloride was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated.

The residue (6.2 g) was pyrolysed with the Kuhrgelrohr distillation apparatus at 150°C under reduced pressure (~1.0 torr), collecting the distillate in an ice-cold trap. The distillate was purified by column chromatography on silica gel. Elution with 10% ether in *n*-hexane gave the diene **28** (1.41 g; 63% yield, based on consumed ketone **33**). Continued elution with 10-30% ether in *n*-hexane gave the ketone **33** (582 mg; 21% recovery).

7α-Acetoxy-2-(1-ethylene)-6β-methyl-1β-bicyclo[4.2.0]oct-2-ene (**29**).

At -78°C, to a solution of ketone **34** (1.07 g, 5.46 mmol) in tetrahydrofuran (30 mL), was added vinylmagnesium bromide (8.0 mL of 1.0 M, 8.0 mmol). After stirring at -78°C and under an atmosphere of nitrogen for 3 h water was added and the resulting mixture warmed to room temperature. A solution of aqueous saturated ammonium chloride was added and the resulting mixture extracted with ether. The ethereal extracts were further washed with water, dried, filtered and concentrated. The residue was dissolved in benzene (50 mL) and cooled to ~5°C. *p*-Toluenesulfonyl isocyanate (1.61 g, 8.19 mmol) was added. After stirring for 2 h ice-cold water was added, followed by aqueous saturated ammonium chloride. The resulting mixture was extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated.

The residue (4.2 g) was pyrolysed in the Kuhrgelrohr apparatus at 120°C under reduced pressure (0.5 torr), collecting the distillate in an ice-cold trap. Purification of the distillate by column chromatography on silica gel, eluting with 10% ether in *n*-hexane gave the pure diene **29** (509 mg; 58% yield, based on consumed starting material):

^{1}Hmr δ6.25 (dd, 1H, J = 17 Hz, J' = 11 Hz, -C<u>H</u>=CH_2), 5.81 (t, 1H, J = 4.5 Hz, -C=CH-), 5.00 to 4.74 (complex m, 3H, -CH=C<u>H_2</u>- and -C<u>H</u>-O-), 2.06 (s, 3H, -$OCOCH_3$) and 1.20 (s, 3H, -C-CH_3); ir (film) 1742 (C=O), 1638 (C=C) and 1600 cm^{-1} (C=C); ms M^+ 206.1301 (Calcd. for $C_{13}H_{18}O_2$: 206.1307). Continued elution with 10-30% ether in <u>n</u>-hexane gave the ketone **34** (170 mg; 16% recovery).

<u>1,4,16β-Triacetoxy-D-nor-14β-estra-1,3,5(10),7-tetraene (**43**)</u>

To a solution of diene **28** (196 mg, 0.95 mmol) and benzoquinone (123 mg, 1.14 mmol) in methylene chloride (10 mL) at -33°C and under an atmosphere of nitrogen was added anhydrous stannic chloride (124 mg, 0.48 mmol). After stirring for 12 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated.

The residue (341 mg) was dissolved in methylene chloride (10 mL). N,N'-Dimethylamino-pyridine (332 mg, 2.71 mmol) and acetic anhydride (2.0 mL) were added. The reaction flask was wrapped with aluminium foil and stirred at room temperature for 20 h. Water was added and the resulting mixture extracted with methylene chloride. The

organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue, eluting with a solution of 20% ethyl acetate in n-hexane gave the triacetate **43** (267 mg, 71% yield): ^{1}Hmr δ6.98, 6.92 (each d, 2H, each J = 10 Hz, aromatic H), 5.55 (m, 1H, -C=CH-), 4.73 (m, 1H, -CH-O-), 3.45 (m, 1H, C-9 H), 3.18 (t, 2H, J = 4.0 Hz, C-6 H), 2.87 (t, 1H, J = 9.0 Hz, C-14 H), 2.36, 2.29 (each s, each 3H, aromatic $-OCOCH_3$), 2.10 (s, 3H, $-OCOCH_3$) and 0.99 (s, 3H, $-C-CH_3$); ir 1762, 1739 (both due to ester C=O); ms M^+ 398.1734 (Calcd. for $C_{23}H_{26}O_6$: 398.1729).

1,4,16α-Triacetoxy-D-nor-14β-estra-1,5(10),7-tetraene (**46**).

To a solution of diene **29** (89 mg, 0.43 mmol) and benzoquinone (70 mg, 0.65 mmol) at -33°C and under an atmosphere of nitrogen, was added anhydrous stannic chloride (56 mg, 0.22 mmol). After stirring for 5 h, the reaction mixture was warmed to room temperature. A solution of aqueous saturated ammonium chloride (50 mL) was added. The resulting mixture was extracted with methylene chloride. the combined organic extracts was further washed with water, dried, filtered and concentrated.

The residue (180 mg) was dissolved in methylene chloride (10 mL). N,N'-Dimethylamino-pyridine (116 mg, 0.95

mmol) and acetic anhydride (220 mg, 2.16 mmol) were added. After stirring for 18 h, water was added and the resulting mixture extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated. Flash chromatography of the residue, eluting with a solution of 30% ether in n-hexane gave the isomeric triacetate **46** (97 mg, 57% yield): ^{1}Hmr δ6.99, 6.96 (each d, 2H, J = 9.0 Hz, 2 x aromatic H), 5.56 (sharp m, 1H, -C=CH-), 4.64 (m, 1H, -CH-O-), 3.36 (m, 1H, C-9 H), 3.20 (sharp m, 2H, C-6 H), 2.38 , 2.32 (each s, 6H, 2 x aryl-OAc), 2.08 (s, 3H, -OAc) and 1.17 (s, 3H, $-C-CH_3$); ir 1763 (C=O) and 1736 cm^{-1} (C=O); ms M^+ 398.1735 (Calcd. for $C_{23}H_{26}O_6$: 398.1730).

16β-Acetoxy-1,4-dimethoxy-D-Nor-14β-estra-1,3,5(10),7-tetraene (**47**).

To a solution of diene **28** (178 mg, 0.86 mmol) and benzoquinone (140 mg, 1.29 mmol) in methylene chloride (10 mL) at -35°C and under an atmosphere of nitrogen, was added anhydrous stannic chloride (112 mg, 0.43 mmol). After stirring for 12 h the reaction mixture was warmed to room temperature. Water was added and the resulting mixtur extracted with methylene chloride. The organic extracts were further washed with water, dried, filtered and concentrated.

The residue was dissolved in acetone (10 mL). Potassium carbonate (597 mg, 4.32 mmol) and methyl iodide (1.23 g, 8.64 mmol) were added. After another 10 h the reaction mixture was cooled to room temperature. Water was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in n-hexane gave an impure acetate **47**. Another pufification of this sample by flash chromatography, eluting with 5% ethyl acetate in n-hexane gave the pure acetate **47** (87 mg; 30% yield): ^{1}Hmr δ6.69, 6.65 (each d, total 2H, each J = 9.0 Hz, 2 x aromatic H), 5.60 (t, 1H, J = 4.0 Hz, -C=CH-), 4.84 (dm, 1H, J = 7 Hz, -CH-O-), 3.84, 3.78 (each s, total 6H, $-OCH_3$), 3.65 (m, 1H, C-9 H), 3.27 (t, 2H, J = 4.0 Hz, 2 x C-6 H), 2.92 (t, 1H, J = 8.0 Hz, C-14 H), 1.15 (S, 3H, -OAc) and 1.04 (s, 3H, $-C-CH_3$); ir 1730 cm^{-1} (C=O); ms M^+ 342.1830 (Calcd. for $C_{21}H_{26}O_4$: 342.1832).

16β-Hydroxy-1,4-dimethoxy-D-Nor-14β-estra-1,3,5(10),7-tetraene (**48**).

Dimethyl ether **47** (62 mg, 0.18 mmol) and potassium carbonate (100 mg, 0.61 mmol) were added to a solution of 50% aqueous methanol. After stirring at room temperature

for 34 h water was added and the resulting mixture extracted with methylene chloride. The organic extracts were washed with water, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether gave the alcohol **48** (36 mg; 67% yield): ^{1}Hmr δ6.67, 6.63 (each d, 2H, each J = 9.0 Hz, 2 x aromatic H), 5.61 (sharp m, 1H, -C=CH-), 4.02 (m, 1H, -C<u>H</u>-O-), 3.74, 3.70 (each s, total 6H, 2 x $-OCH_3$), 3.54 (m, 1H, C-9 H), 3.28 (sharp m, 2H, C-6 H), 2.98 (t, 1H, J = 10 Hz, C-14 H) and 1.09 (s, 3H, $-C-CH_3$); ir 3370 (-OH); ms M^+ 300.1723 (Calcd. for $C_{19}H_{24}O_3$: 300.1731).

<u>1,4-Dimethoxy-16-oxo-D-Nor-14β-estra-1,3,5(10),7-tetraene (**51**)</u>.

To a solution of oxalyl chloride (8.0 mg, 0.06 mmol) and dimethylsulfoxide (8.0 mg, 0.10 mmol) in methylene chloride (5 mL) at -78°C and under an atmosphere of nitrogen, was added a solution of alcohol **48** (15 mg, 0.05 mmol) in methylene chloride (2 mL). After warming the reaction mixture to -10°C, triethylamine (0.5 mL) was added. After stirring for 8 h water was added and the resulting mixture was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue, eluting

with 15% ether in n-hexane gave the pure cyclobutanone **51** (10.1 mg; 69% yield): ^{1}Hmr δ6.59, 6.56 (each d, total 2H, each J = 8.0 Hz, 2 x aromatic H), 5.66 (sharp m, 1H, -C=CH-), 3.71, 3.69 (each s, total 6H, 2 x $-OCH_3$), 3.52 (m, 1H, C-9 H), 3.43, 2.87 (each dd, each 1H, each J = 16 Hz, J' = 8.0 Hz, 2 x C-15 H), 3.21 (sharp m, 2H, 2 x C-6 H), 2.70 (t, 1H, J = 8.0 Hz, C-14 H) and 1.13 (s, 3H, $-C-CH_3$); ir 1776 (C=O), 1600 cm^{-1} (aromatic C=C); ms M^+ 198.1567 (Calcd. for $C_{19}H_{22}O_3$: 298.1569).

16α-Acetoxy-1,4-dimethoxy-D-Nor-14β-estra-1,3,5(10),7-tetraene (**49**).

Diene **29** (283 mg, 1.37 mmol) and benzoquinone (742 mg, 6.06 mmol) were placed in methylene chloride (20 mL) and cooled to -30°C. Anhydrous stannic chloride (179 mg, 0.69 mmol) was added. After stirring under an atmosphere of nitrogen for 5 h, the reaction mixture was warmed to room temperature. Water was added and the resulting mixture was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated.

The residue was dissolved in acetone (20 mL). Potassium carbonate (1.90 mg, 13.7 mmol) and methyl iodide (3.90 g, 27.8 mmol) were added and heated to reflux. After 15 h, the reaction mixture was cooled to room temperature.

Water was added and the resulting mixture was extracted with methylene chloride. The combined organic extracts were dried, filtered and concentrated. Flash chromatography of the residue, eluting with a solution of 20% ethyl acetate in n-hexane gave the dimethyl ether **49** (103 mg; 22% yield): ^{1}Hmr δ6.62, 6.57 (each d, each 1H, each J = 9.0 Hz, 2 x aromatic H), 5.52 (tm, 1H, J = 3.0 Hz, -C=CH-), 4.53 (m, 1H, -CH-O-), 3.76, 3.70 (each s, total 6H, 2 x $-OCH_3$), 3.45 (m, 1H, C-9 H), 3.18 (t, 2H, J = 3.0 Hz, C-6 H), 2.01 (s, 3H, -OAc) and 1.09 (s, 3H, $-C-CH_3$); ir 1736 cm^{-1} (C=O); ms M^+ 342.1829 (Calcd. for $C_{21}H_{26}O_4$: 342.1831).

16β-Hydroxy-1,4-dimethoxy-D-Nor-14β-estra-1,3,5(10),7-tetraene (**50**).

Dimethyl-ether **49** (79 mg, 0.23 mmol) and potassium carbonate (159 mg, 1.15 mmol) were placed in a solution of 50% aqueous methanol (5 mL). After stirring for 17 h, water was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue, eluting with 20% ethyl acetate in petroleum ether gave the alcohol **50** (55 mg; 80% yield): ^{1}Hmr δ6.63, 6.60 (each d, 2H, J = 9.0 Hz), 2 x aromatic H), 5.51 (sharp m, 1H, -C=CH-), ~3.90 (m, 1H, -CH-OH), 3.27, 3.73 (each s, 6H, 2 x $-OCH_3$), 3.48

(m, 1H, C-9 H), 3.20 (t, 2H, J = 4.0 Hz, C-6 H) and 1.06 (S, 3H, $-C-CH_3$); ir 3380 cm^{-1} (-OH); ms M^+ 300.1721 (Calcd. for $C_{19}H_{24}O_3$: 300.1725).

1,4-Dimethoxy-16-oxo-D-Nor-14β-estra-1,3,5(10),7-tetraene (**51**).

To a solution of oxalyl chloride (21 mg, 0.17 mmol) and dimethylsulfoxide (13 mg, 0.17 mmol) in methylene chloride at -78°C and under an atmosphere of nitrogen, was added a solution of the alcohol **50** (42 mg, 0.14 mmol) in methylene chloride (2.0 mL). After warming the reaction mixture to -10°C, triethylamine (0.5 mL) was added. After stirring for another 8.0 h, water was added and the resulting mixture extracted with methylene chloride. The combined organic extracts was dried, filtered and concentrated. Purification by column chromatography on silica gel gave the pure cyclobutanone derivative **51** (34 mg, 82% yield) which was identical in spectral data (^{1}Hmr and ir) to the cyclobutanone derivative obtained previously (vide supra).

A 1:1:1 mixture of Diels-Alder adducts **Ia**, **Ib** and **Ic**.

At -30°C, anhydrous stannic chloride (238 mg, 0.92 mmol) was added to a solution of enone-ester (563 mg, 3.66

mmol) and diene **28** (377 mg, 1.83 mmol). After stirring under an atmosphere of nitrogen for 12 h the reaction mixture was warmed to room temperature and water was added. The resulting mixture was extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ether in n-hexane gave a 1:1 mixture of **Ia** and **Ib** (343 mg; 52% yield). The ^{1}Hmr spectrum of the mixture showed two sets of signals in an integral ratio of 1:1 and showed signals at δ5.30 (m, 1H, -C=CH-), 4.85 (t, ~0.5H, J = 8.0 Hz, -CH-O-), 4.67 (m, ~0.5H, -CH-O-), 3.82, 3,74 (each s, total 3H, $-COOCH_3$), 2.10, 2.04 (each s, total 3H, $-OCOCH_3$) and 1.18, 1.07 (each s, total 3H, $-C-CH_3$); ir 1735 (ester C=O) and 1716 cm^{-1} (ketone C=O); ms M^+ 360.1985 (Calcd. for $C_{21}H_{28}O_5$: 360.1936). Continued elution gave a single adduct **Ic** (171 mg; 26% yield): ^{1}Hmr δ5.35 (m, 1H, -C=CH-), 4.85 (m, 1H, -CH-O-), 3.76 (s, 3H, $-COOCH_3$), 3.05 (m, 1H, C-9 H), 2.10 (s, 3H, $-OCOCH_3$) and 0.98 (s, 3H, $-C-CH_3$); ir 1736 (ester C=O) and 1718 cm^{-1} (ketone C=O); ms M^+ 360.1955 (Calcd. for $C_{21}H_{28}O_5$: 360.1936).

Alcohols **IIa** and **IIb**.

The 1:1 mixture of Diels-Alder adducts **Ia** and **Ib** (121 mg, 0.34 mmol) and potassium carbonate (232 mg, 1.68 mmol)

were dissolved in a solution of 50% aqueous methanol. After stirring for 2 h, water was added and the resulting mixture extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 20% ether in n-hexane gave a single alcohol **IIa** (39 mg; 37% yield): ^{1}Hmr δ5.28 (m, 1H, -C=CH-), 3.81 (m, 1H, -CH-O-), 3.79 (s, 3H, $-COOCH_3$) and 1.08 (s, 3H, $-C-CH_3$); ir 3300 (-OH), 1735 (ester C=O) and 1717 cm^{-1} (ketone C=O); ms M^+ 318.1832 (Calcd. for $C_{29}H_{26}O_4$: 318.1832). Continued elution with 20-30°C ether in n-hexane gave **IIb** (50 mg, 47% yield): ^{1}Hmr δ5.22 (m, 1H, -C=CH-), 3.90 (m, 1H, J = 8.0 Hz, -CH-O-), 3.66 (s, 3H, $-COOCH_3$) and 1.07 (s, 3H, $-C-CH_3$); ir 3400 (-OH), 1716 cm^{-1} (broad, C=O); ms M^+ 318.1829 (Calcd. for $C_{19}H_{26}O_4$: 318.1832).

Alcohol **IIc**.

Diels-Alder adduct **Ic** (15 mg, 0.042 mmol) and potassium carbonate (30 mg, 0.21 mmol) were dissolved in a solution of 50% aqueous methanol. After stirring for 2 h the reaction mixture was diluted with water and extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 40% ethyl acetate in n-hexane gave

the pure alcohol **IIc** (12 mg; 91% yield): ^{1}Hmr δ5.33 (sharp m, 1H, -C=CH-), 3.97 (m, 1H, -CH-O-), 3.75 (s, 3H, $-COOCH_3$), 3.00 (dm, J = ~12 Hz, C-9 H), 2.78 (t, 1H, J = 9.0 Hz, C-14 H) and 1.01 (s, 3H, $-C-CH_3$); ir 3420 (-OH), 1744 (ester C=O) and 1714 cm^{-1} (ketone C=O); ms M^+ 318.1842 (Calcd. for $C_{19}H_{26}O_4$: 318.1831).

Cyclobutanone derivative **55**.

Alcohol **IIc** (11 mg, 0.03 mmol) was placed in acetone (2 mL) and cooled to 0°C. Jone's reagent (0.5 mL of 8 N, 4.0 mmol) was added. Water was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue, eluting with 15% ethyl acetate in n-hexane gave the cyclobutanone derivative **55** (8 mg, 73% yield) which was recrystallized from a solution of ether in n-hexane to give white crystals of pure **55**, m.p. 142-144°C: ^{1}Hmr δ5.53 (m, 1H, -C=CH-), 3.72 (s, 3H, $-COOCH_3$), 3.49, 311 (each dd, each 1H, each J = 18 Hz), J' = 8.0 Hz, 2 x C-15 H) and 1.17 (s, 3H, $-C-CH_3$); ir 1775 (cyclobutanone C=O), 1740 (ester C=O) and 1716 cm^{-1} (cyclohexanone C=O); ms M^+ 316.1669 (Calcd. for $C_{19}H_{24}O_4$: 316.1674).

A ~1:1:1 mixture of Cyclobutanone derivatives **58**.

A 1:1:1 mixture of Diels-Alder adducts **Ia**, **Ib** and **Ic** (112 mg, 0.31 mmol) and potassium carbonate (500 mg, 3.62 mmol) were dissolved in a solution of 50% aqueous methanol (10 mL). After stirring for 16 h water was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated to give the ~1:1:1 mixture of alcohols **IIa**, **IIb** and **IIc**. Without purification the mixture of alcohols (125 mg) in methylene chloride (10 mL) was added to a solution of oxalyl chloride (47.6 mg, 0.38 mmol) and dimethylsulfoxide (58.6 mg, 0.75 mmol) in methylene chloride (10 mL) at -78°C. After stirring under an atmosphere of nitrogen for 1.5 h the reaction mixture was warmed to ~10°C. Triethylamine (1 mL) was added. After another 4 h saturated aqueous ammonium chloride was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 40% ether in n-hexane gave the ~1:1:1 mixture of cyclobutanone derivative **58** (71 mg; 72% yield). The ^{1}Hmr spectrum showed three sets of signals in an integral ratio ~1:1:1. One set of signals was similar to those reported for the single cyclobutanone derivative **55**. The other two sets of signals showed at

δ5.50, 5.38 (each m, total 1H, -C=CH-), 3.80, 3.73 (each s, total 3H, $-COOCH_3$) and 1.27, 1.11 (each s, total 3H, $-C-CH_3$). The following spectral data were also recorded for the ~1:1:1 mixture of **58**: ^{13}Cmr δ212.4, 206.3, 206.1, 173.8, 171.0, 137.6, 135.3, 134.1, 120.9, 120.0, 119.3, 104,9, 52.4, 52.1, 49.6, 49.0, 48.0, 40.8, 40.7, 40.1, 39.7, 39.6(9), 38.6, 38.1, 35.4, 34.9, 33.1, 30.3, 30.1, 28.7, 28.5, 26.9, 26.8, 26.5, 26.4, 26.0, 25.5, 24.3, 23.5, 23.2, 23.0, 21.9, 21.4, 20.7 and 19.9; ir 1775 (cyclobutanone C=O), 1740 (ester C=O) and 1716 cm^{-1} (cyclohexanone C=O); ms M^+ 316.1676 (Calcd. for $C_{19}H_{24}O_4$: 316.1674).

A 1:1:0.3 Mixture of Diels-Alder adducts **53a**, **53b** and **53c**.

At -30°C, anhydrous stannic chloride (88.5 mg, 0.34 mmol) was added to a solution of enone-ester **20** (109 mg, 1.36 mmol) and diene **29** (140 mg, 0.68 mmol) in methylene chloride. After stirring under an atmosphere of nitroegn for 10 h, the reaction mixture was warmed to room temperature and water was added. The resulting solution was extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in n-hexane gave a ~1:1:0.3 mixture of three adducts **53a**, **53b** and **53c** (165 mg; 68% yield).

The ^{1}Hmr spectrum of the mixture showed three sets of signals in an integral ratio of ~1:1:0.3 and showed signals at δ5.37, 5.30, 5.22 (each m, total 1H, -C=CH-), 4.71, 4.57 (each m, total 1H, -CH-O-), 3.75, 3.71, 3.69 (each s, total 3H, $-COOCH_3$), 2.01, 2.00, 1.98 (each s, total 3H, $-OCOCH_3$) and 1.26, 1.16, 1.10 (each s, total 3H, $-C-CH_3$); ir 1735 (ester C=O) and 1718 cm^{-1} (ketone C=O); ms M^+ 360.1950 (Calcd. for $C_{21}H_{28}O_5$: 360.1936).

A ~1:1:0.3 Mixture of alcohols **57a**, **57b** and **57c**.

A 1:1:0.3 mixture of adducts **56a**, **56b** and **56c** (47 mg, 0.130 mmol) and potassium carbonate (90 mg, 0.65 mmol) were added to a solution of 50% aqueous methanol (10 mL). After stirring for 10 h water was added and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 30% ethyl acetate in n-hexane gave a ~1:1:0.3 mixture of alcohols **57a**, **57b** and **57c** (34 mg; 81% yield). The ^{1}Hmr spectrum showed three sets of signals in an integral ratio of ~1:1:0.3 and showed signals at δ5.32, 5.26, 5.20 (each m, total 1H, -C=CH-), 3.92 to 3.80 (complex m, total 1H, -CH-O-), 3.76, 3.75, 3.73 (each s, total 3H, $-COOCH_3$) and 1.23, 1.11, 1.08 (each s, total 3H, $-C-CH_3$); ir 3420 (-OH), 1710 (ester C=O) and 1714

cm^{-1} (ketone C=O); ms M^+ 318.1838 (Calcd. for $C_{19}H_{24}O_4$: 318.1831.

A ~1:1:0.3 Mixture of cyclobutanone derivatives **55**.

A mixture of alcohols **57a**, **57b** and **57c** (34 mg, 0.11 mmol) was dissolved in acetone (2 mL) and cooled to 0°C. Jone's reagent (0.5 mL of 8.0 N 4.0 mmol) was added. The resulting mixture was diluted with water and extracted with methylene chloride. The organic extracts were combined, dried, filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with 15% ethyl acetate in n-hexane gave the ~1:1:0.3 mixture (by ^{1}Hmr analysis) of cyclobutanone derivatives **55** (20 mg, 59% yield) which showed similar ^{1}Hmr, ^{13}Cmr and ir spectra to those of the cyclobutanone derivatives obtained previously from the ~1:1:1 mixture of alcohols **IIa**, **IIb** and **IIc** (vide supra). In this case, the ^{1}Hmr spectrum of the minor component showed signals at δ5.37 (m, 1H, -C=CH-), 3.75 (s, 3H, $-COOCH_3$) and δ1.30 (s, 3H, $-C-CH_3$).

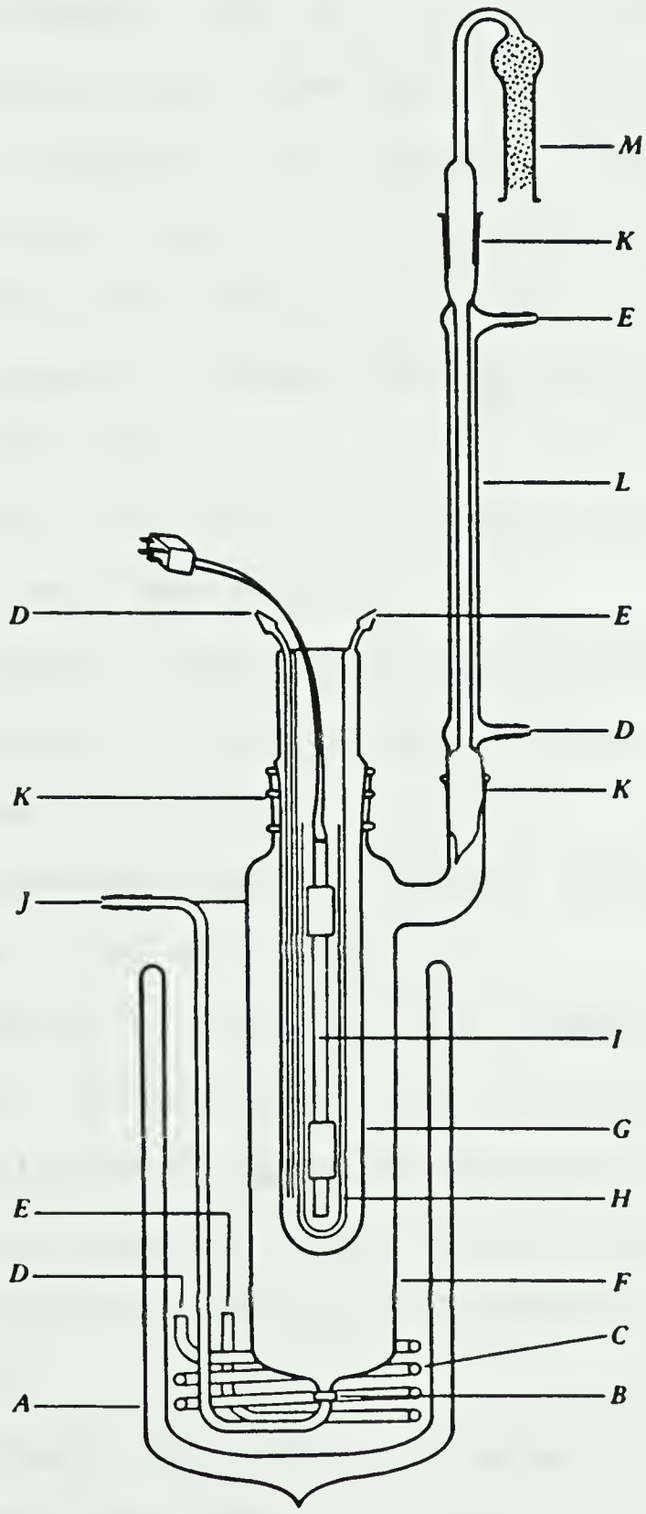

Figure 1. *A*, Dewar flask; *B*, sintered glass filter; *C*, metal cooling coil; *D*, water inlet; *E*, water outlet; *F*, reaction vessel; *G*, quartz immersion well; *H*, pyrex filter; *I*, lamp; *J*, nitrogen gas inlet; *K*, ground glass joint; *L*, condenser; *M*, calcium chloride drying tube.

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